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Nickel-catalyzed cross-coupling of unactivated alkyl halides and tosylate carrying a functional group with alkyl and phenyl Grignard reagents

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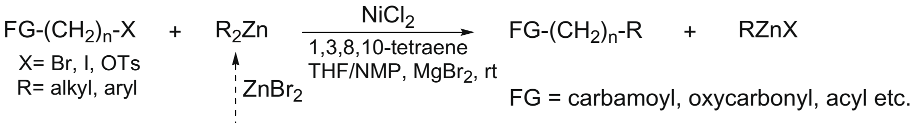
ABSTRACT

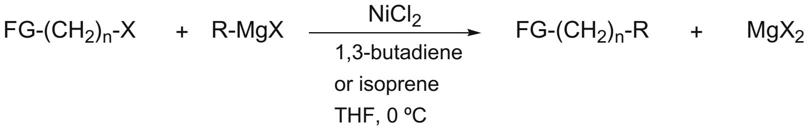
By the use of catalytic amounts of a nickel salt and a 1,3-butadiene, primary and secondary alkyl Grignard reagents undergo cross-coupling with alkyl bromides, iodide, and tosylate carrying a functional group such as amide, ester, and ketone at 0 °C in THF. The present procedure provides a simple, convenient, and practical method for construction of carbon chains in the presence of various functional groups. PhMgBr also gave the corresponding coupling product in a moderate yield.

Transition-metal catalyzed cross-coupling reaction of organic halides with organometallic reagents is one of the most powerful tools for constructing new carbon–carbon bonds. With the use of mild nucleophiles such as organozinc, -boron, and -silicon compounds, functionalized substrates can be employed as the coupling partners.[1] During the course of our studies on Ni-catalyzed alkylation reactions,[2] we have revealed that bisdienes (1,3,8,10-tetraenes) showed remarkable effect as the ligand precursors for alkyl–alkyl cross-coupling of alkyl halides carrying a carbonyl functionality with dialkylzincs prepared in situ from $ZnBr_2$ and the corresponding RMgX (Eq. 1).[2c] This procedure is operationally simple and gives good yields of amides, esters, and ketones with extended carbon chains. However, one drawback of this procedure is that only one of the alkyl group on Zn can be transferred efficiently, that is, alkylzinc halides (RZnX) generating from dialkylzincs via alkyl group transfer do not work as an effective nucleophile in this system. In order to achieve highly atom economical cross-coupling we examined the scope and limitation of Ni-catalyzed cross-coupling of Grignard reagents with alkyl halides and a tosylate in the presence of a simple diene and found that this catalytic system is tolerant toward amide, ester, and ketone functionalities (Eq. 2).



$$\underset{\substack{X = Br, I, OTs\\ R = alkyl, aryl}}{FG\text{-}(CH_2)_n\text{-}X} + \underset{\substack{\uparrow\\ ZnBr_2}}{R_2Zn} \xrightarrow[\substack{1,3,8,10\text{-tetraene}\\ THF/NMP,\ MgBr_2,\ rt}]{NiCl_2} FG\text{-}(CH_2)_n\text{-}R + RZnX \qquad (1)$$

FG = carbamoyl, oxycarbonyl, acyl etc.



$$FG\text{-}(CH_2)_n\text{-}X + R\text{-}MgX \xrightarrow[\substack{1,3\text{-butadiene}\\ \text{or isoprene}\\ THF,\ 0\ ^{\circ}C}]{NiCl_2} FG\text{-}(CH_2)_n\text{-}R + MgX_2 \qquad (2)$$

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
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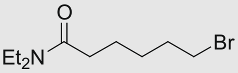
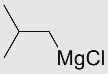
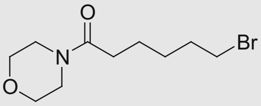
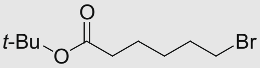
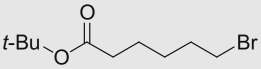
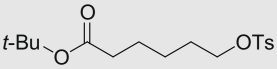
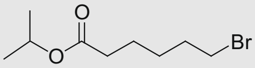
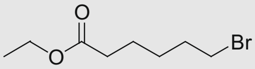
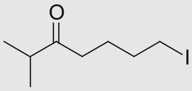
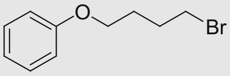
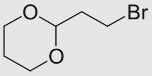
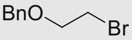
Table 1
Cross-coupling of functionalized unactivated alkyl halides and tosylate with Grignard reagents

Entry	Alkyl halide	Grignard reagent	NiX_2 (mol %)	Isolated (GC) yield (%)
1		*n*-BuMgCl	$NiCl_2$ (1)	(100)[a]
2		*n*-BuMgCl	Ni(acac)$_2$ (1)	(99)
3		*n*-BuMgCl	$NiBr_2$ (1)	(90)
4		*n*-BuMgCl	$NiCl_2$ (1)	(98)[b]
5		*n*-OctMgCl	$NiCl_2$ (1)	81
6			$NiCl_2$ (1)	93
7		*i*-PrMgC	$NiCl_2$ (5)	79
8		*s*-BuMgBr	$NiCl_2$ (5)	83
9		PhMgBr	$NiCl_2$ (1)	51
10		*n*-BuMgCl	$NiCl_2$ (1)	80
11		*i*-PrMgCl	$NiCl_2$ (5)	72
12		*n*-BuMgCl	$NiCl_2$ (3)	93
13		*n*-BuMgCl	$NiCl_2$ (3)	78[c]
14		*n*-BuMgCl	$NiCl_2$ (1)	83
15		*i*-PrMgCl	$NiCl_2$ (5)	83
16		*n*-BuMgCl	$NiCl_2$ (5)	79
17		*n*-BuMgCl	$NiCl_2$ (1)	11
18			Ni(acac)$_2$ (5)	72[d]
19		*n*-BuMgCl	$NiCl_2$ (3)	97
20		*n*-BuMgCl	$NiCl_2$ (3)	86
21		*n*-BuMgCl	$NiCl_2$ (3)	88

Conditions: alkyl halide or tosylate (1 mmol), Grignard reagent (1.1 mmol), butadiene (0.2 mmol, 20 mol %), NiX_2, THF, 0 °C, 1 h except otherwise stated.

[a] 10 min.

[b] Isoprene was used as an additive.

[c] 30 mol % of 1,3-butadiene was used, 1.5 h.

[d] 10 °C.

Several combinations of functionalized unactivated alkyl bromides, iodide, and tosylate with alkyl and phenyl Grignard reagents were examined. As the polar functionalities, amide, ester, ketone as well as acetal and ether groups were chosen and the results are summarized in Table 1.

Amide groups react only slowly with Grignard reagents[3] and haloalkanamides gave good to excellent yields of cross-coupling products by the reaction with primary and secondary alkyl Grignard reagents in the presence of a Ni salt and 1,3-butadiene (runs 1–3, 5–8, 10).[4] GC analysis of these resulting mixtures showed complete consumption of starting materials and no other large peaks were observed except desired products. Isoprene also showed a remarkable activity as a ligand precursor (run 4). Under identical conditions, phenyl Grignard reagent afforded a moderate yield (51%) of the desired product and 13% of biphenyl as a byproduct with recovery of 22% of the halide used (run 9). Bromides and tosylate carrying *tert*-butyl or isopropyl ester groups also gave alkylated products in good yields with butyl or isopropyl Grignard reagents (runs 11–15). Unfortunately, reaction of isopropyl 6-bromohexanoic acid ester with secondary and tertiary butyl Grignard reagent did not afford cross-coupling products.[5] The corresponding ethyl ester reacted with butyl Grignard reagent to afford only 11% yield of the coupling product with 1 mol % of Ni catalyst, probably due to the relatively fast direct addition of the Grignard reagent at the carbonyl carbon. However, this problem was overcome by using 5 mol % of NiCl$_2$ to accelerate the coupling process (runs 16 and 17). When an iodide was employed, even ketone group can tolerate the present catalytic conditions to furnish the cross-coupling predominantly (run 18). Under the same conditions, acetal and ether groups did not affect the present cross-coupling reaction (runs 19–21).

As demonstrated above, the present nickel/butadiene catalyst system can successfully be applied to direct cross-coupling reaction of primary and secondary alkyl and phenyl Grignard reagents with functionalized alkyl halides and tosylate. This compatibility arises from high catalytic activity of nickelate complexes as nucleophiles toward sp^3 carbons and the subsequent rapid reductive elimination of the resulting Ni(IV) intermediates.[2]

Knochel and co-workers have pioneered the development of methods for the preparation of functionalized aryl or vinyl Grignard reagents and applied directly, or via transmetallation to more stable organometallic reagents, to cross-coupling reaction.[6] Although several interesting reactions have been reported to couple functionalized organic halides with Grignard reagents,[7] only three catalytic systems of alkyl–alkyl cross-coupling have been developed by the aid of N-based pincer ligands or excess NMP.[8] The present reaction proceeds with only 1–5 mol % of NiCl$_2$ and 20 mol % of a 1,3-butadiene as an additive without such heteroatom ligands, and would provide a simple, convenient, and practical method for construction of carbon chains in organic synthesis.

Acknowledgments

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1. (a) For recent reviews, see for example: *Catalytic Components for Coupling Reactions*; Molander, G. A., Ed.; John Wiley & Sons Ltd: West Sussex, 2008; (b) Lipshutz, B. H.; Ghorai, S. *Aldrichim. Acta* **2008**, *41*, 57–72; (c) Negishi, E.-I.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474–1485; (d) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486–1499; (e) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–325; (f) Demmart, S. D.; Baird, J. D. *Chem. Eur. J.* **2006**, *12*, 4954–4963.
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3. *N*,*N*-Diethyl-pentanamide reacted slowly with *n*-BuMgCl in the absence of Ni catalyst and butadiene at 0 °C in THF to form dibutyl ketone as a major product in 10% yield in 1 h and 40% yield in 7 h.
4. A typical experiment is as follows. A dry nitrogen-flushed 50-mL flask equipped with a stirring bar and a rubber septum was charged with anhydrous THF (0.3 mL), 6-bromo-*N*,*N*-diethylhexanamide (250.18 mg, 1 mmol) and cooled to −78 °C. Then ^{n}BuMgCl (0.6 mL, 1.82 M in THF, 1.1 mmol) (slowly) and 1,3-butadiene (4.5 ml at 20 °C under 1 atm) and NiCl$_2$ (1.3 mg, 1 mol %) were added. The reaction mixture was warmed up to 0 °C and stirred for 10 min. Then the reaction was quenched with aqueous HCl (1 N, 5 mL). The aqueous phase was extracted with ether (3 × 15 mL). The combined organic layers were dried with MgSO$_4$, and evaporated to give a colorless crude product (100% by GC). Purification by HPLC (using JAIGEL-2H and JAIGEL-1H column) with CHCl$_3$ as an eluent afforded 223 mg (98%) of *N*,*N*-diethyldecanamide as a colorless oil.
5. *sec*-BuMgBr attacked ester group predominantly giving a complex mixture which may contain a small amount of desired coupling product. Reactions using a mixture of *i*-Pr and *sec*-Bu Grignard reagents afforded a coupling product only from *i*-Pr Grignard reagent. In the case of *t*-BuMgCl, most of the starting material (ca. 96%) remained unchanged due probably to the slow reaction toward both ester and bromoalkyl groups under the conditions employed.
6. (a) Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 205–209; (b) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802–6806; (c) Hiriyakkanavar, I.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583–593; (d) Knochel, P.; Krasovskiy, A.; Sapountzis, I.. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, pp 109–172; (e) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320.
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