An Efficient and Stereoselective Synthesis of Homoallylic Alcohols *via* Nickel-catalysed Coupling of 5-Alkyl-2,3-dihydrofurans with Grignard Reagents

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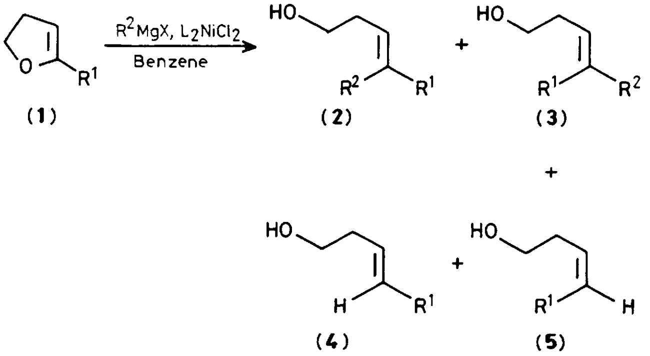
The low-valent nickel-catalysed coupling of Grignard reagents with 5-alkyl-2,3-dihydrofurans is an efficient and stereoselective method for synthesising homoallylic alcohols provided appropriate care is taken in the workup.

In 1979 Wenkert and co-workers[1] showed that enol ethers and Grignard reagents undergo coupling mediated by low-valent nickel species generated by the reaction of $NiCl_2$–phosphine complexes with Grignard reagents. The reaction of 5-methyl-2,3-dihydrofuran (**1**), (R^1 = Me) with a variety of Grignard reagents was examined in some detail and it was shown that the course of the reaction depended on the catalyst and the structure of the Grignard reagent.[2] For example, with EtMgBr a mixture of coupling products (**2**) and (**3**) (R^1 = Me, R^2 = Et) and reduction products (**4**) and (**5**) (R^1 = Me) was generated in which the ratio (**2**) + (**3**) : (**4**) + (**5**) varied from 1:7 with $(PPh_3)_2NiCl_2$ to 4:1 with $\{Ph_2P[CH_2]_2PPh_2\}NiCl_2$. In general, the products (**2**) and (**4**) with retained stereochemistry predominated. We have examined the Wenkert reaction with a broader repertoire of 5-alkyl-2,3-dihydrofurans, Grignard reagents, and catalysts and now present some observations on the scope and stereochemistry of the reaction which suggests that it provides an efficient and highly stereoselective method for the preparation of homoallylic alcohols containing tri-substituted double bonds.



The potential of the Wenkert reaction for the large scale preparation of homoallylic alcohols and the crucial importance of workup procedure are illustrated by the reaction of MeMgBr with dihydrofuran (**8**) which was prepared by the alkylation of 5-lithio-2,3-dihydrofuran (**7**)[3] as shown in Scheme 1.

The following procedure is representative. To bis(triphenylphosphine)nickel(II) dichloride (6.85 g, 10.5 mmol) in dry benzene (150 ml) under argon at room temperature was added dropwise methylmagnesium bromide (17.0 ml, 3 M in diethyl ether, 51 mmol). After stirring for 15 min at room temperature more methylmagnesium bromide (70 ml of 3 M solution, 210 mmol) was added before the majority of the solvent was removed *in vacuo* by rotary evaporation. The residue was suspended in benzene (200 ml) and 2,3-dihydro-5-(hex-5-enyl)furan (**8**) (15.9 g, 105 mmol) in benzene (20 ml) added.

The mixture was refluxed for 45 min, cooled to 0 °C and quenched by pouring as a slow stream into vigorously stirred saturated aqueous ammonium chloride solution (350 ml) at 0 °C. The stirring was continued for 20 min before the organic layer was separated and the aqueous phase extracted with diethyl ether (4 × 200 ml). The combined organic layers were dried ($MgSO_4$), the solvent removed, and the residue chromatographed on silica (diethyl ether : light petroleum 1 : 3—1 : 1 as eluant) to remove biphenyl impurity. Kugelrohr distillation (200 °C/14 mmHg) gave the alcohol (**9**) (16.8 g, 96%) as a colourless oil. Gas chromatography (6% OV 101 on chromosorb, 150 °C) indicated that the product was >99% (*E*)-isomer.

If the aqueous quench was slower or stirring inefficient, substantial amounts of isomeric products (**10**) were formed in which the C-3–C-4 double bond had isomerised and the terminal alkene had rearranged one carbon into the chain (*E*- and *Z*-isomers). When the quench was performed by slowly adding water to the reaction mixture, these isomeric products (**10**) accounted for >80% of the reaction mixture. These experiments suggest that a low-valent nickel catalyst is generated on addition of water which can rapidly and efficiently promote rearrangement and isomerisation of double bonds and that this same catalyst can be destroyed by the simple expedient of rapid and efficient stirring in the workup.

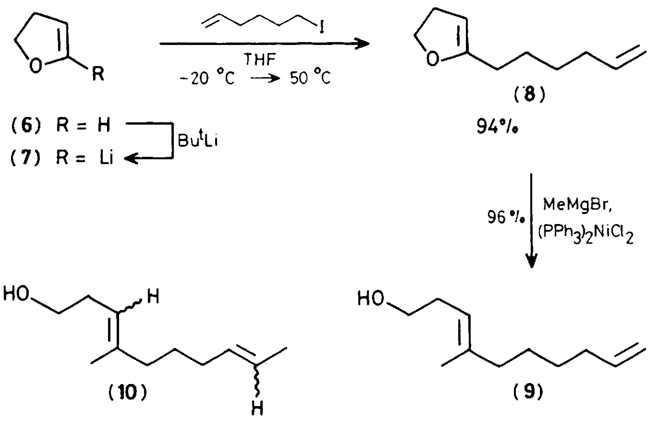
Table 1. Coupling products from the nickel-catalysed reaction of dihydrofurans with Grignard reagents lacking β-hydrogens.[a]

Entry	R^1	R^2	Catalyst[b]	Time	Yield (**2**)/%[c]
1	H	Me	C	20 min	78[d]
2	Me	Me	C	30 min	78[d]
3	Me	Ph	A	20 min	85
4	Me	$PhCH_2$	A	1 h	91
5	Me	Me_3SiCH_2[e]	B	1.5 h	85
6	Pr^n	Me	A	20 min	79
7	Pr^n	Ph	A	20 min	83
8	n-Pentyl	Me	A	20 min	87
9	n-Pentyl	Me	C	30 min	76
10	n-Pentyl	Ph	A	20 min	92
11	n-Pentyl	$PhCH_2$	A	1 h	79
12	n-Pentyl	Me_3SiCH_2[e]	B	1.7 h	77
13[f]	n-Hex-5-enyl	Me	A	45 min	96

[a] All reactions were conducted in refluxing benzene on a 2 mmol scale using organomagnesium bromides unless otherwise specified. [b] A = $(Ph_3P)_2NiCl_2$; B = $\{Ph_2P[CH_2]_3PPh_2\}NiCl_2$; C = $\{Ph_2P[CH_2]_2PPh_2\}NiCl_2$. [c] Yield of chromatographically purified and distilled products unless otherwise specified. [d] Yield of chromatographically purified benzoate derivative. [e] Organomagnesium chloride used. [f] 105 mmol scale.

Table 1 gives the results of the reaction of 5-alkyl-2,3-dihydrofurans (**1**) (R^1 = H, Me, n-propyl, and n-pentyl) with Grignard reagents lacking β-hydrogens. In general the reactions were over in less than 1 h in refluxing benzene and gave coupling products (**2**) in good yield with ≥95% retention of configuration. $(PPh_3)_2NiCl_2$ was the catalyst of choice because it is cheap and gave the fastest rate of reaction.

In contrast to the results in Table 1, the reaction of (**1**) (R^1 = H, Me, n-propyl, n-pentyl) with Grignard reagents bearing β-hydrogens (Table 2) was complicated by the competing formation of reduction products (**4**) and (**5**). Although the reduction reaction usually gave a mixture of (**4**) and (**5**), the



THF = tetrahydrofuran

Scheme 1

Table 2. Coupling and reduction products from the nickel-catalysed reaction of dihydrofurans with Grignard reagents bearing β-hydrogens.[a]

Entry	R^1	R^2	Catalyst[b]	Time/h	Yield (**2**) + (**4**) + (**5**)/%[c]	Ratio (**2**) : (**4**) + (**5**)[d,e]
1	H	Bu^n	C	20	62	>95 : 5
2	Me	Et	A	18	51	0 : 100[f]
3	Me	Et	B	25	75	5 : 1[f]
4	Me	Et	C	26	78	7 : 1[f]
5	Me	Et	D	4	68	4 : 1[f]
6	Me	Pr^n	C	20	68	4 : 1
7	Me	Bu^n	C	21	73	5 : 1
8	Me	Bu^i	C	20	40	1 : 1[g]
9	Pr^n	Et	B	26	73	4 : 1
10	Pr^n	Et	C	28	82	5 : 1
11	n-Pentyl	Et	B	26	79	3 : 1
12	n-Pentyl	Et	C	28	80	5 : 1
13	n-Pentyl	Et	D	4.5	80	3 : 2
14	n-Pentyl	Bu^n	C	20	82	>95 : 5

[a] All reactions were conducted in refluxing benzene on a 2 mmol scale using organomagnesium bromides. [b] A = $(Ph_3P)_2NiCl_2$; B = $\{Ph_2P[CH_2]_3PPh_2\}NiCl_2$; C = $\{Ph_2P[CH_2]_2PPh_2\}NiCl_2$; D = [1,1′-bis(diphenylphosphino)ferrocene]$NiCl_2$. [c] Yield of chromatographically purified mixture. [d] Ratio determined by n.m.r. spectroscopy unless otherwise specified. [e] Ratio of (**4**) : (**5**) was not determined. [f] Ratio determined by g.c. [g] The coupling product was a 2 : 1 mixture of *E*- and *Z*-isomers.

coupling reaction invariably proceeded with $\geqslant 95\%$ stereoselectivity with retention of configuration to give (**2**). From the data presented in Table 2 three important trends emerge. First, the coupling of Grignard reagents bearing β-hydrogens was notably slower than the corresponding coupling of Grignard reagents lacking β-hydrogens. Secondly, the ratio of coupling to reduction depended on the catalyst. For example, in the case of the reaction of (**1**) (R^1 = Me) with EtMgBr (entries 2—5) $(PPh_3)_2NiCl_2$ gave exclusively reduction whereas coupling was maximised with $\{Ph_2P[CH_2]_2PPh_2\}NiCl_2$. In the reaction of EtMgBr with (**1**) (R^1 = n-propyl) (entries 9 and 10) and (**1**) (R^1 = n-pentyl) (entries 11—13) $\{Ph_2P[CH_2]_2PPh_2\}NiCl_2$ was again the catalyst of choice. Finally, with the exception of [1,1′-bis(diphenylphosphino)ferrocene]$NiCl_2$ (entry 13), the overall rate of reaction did not vary significantly with catalyst, Grignard reagent, or substitution on the dihydrofuran.

There are some important limits to the reaction. Vinylmagnesium bromide failed to couple with (**1**) (R^1 = n-pentyl) and allylmagnesium chloride gave complex mixtures resulting from double bond rearrangement of the initial coupling products to conjugated dienes. Primary Grignard reagents with branching substituents on the α-position couple inefficiently and give substantial amounts of reduction (Table 2, entry 8). However, it is noteworthy that coupling of a bulky Grignard reagent with a dihydrofuran with a bulky side chain (Table 2, entry 14) is efficient, highly stereoselective, and remarkably free of competing reduction.

Provided care is taken in the workup, the nickel-catalysed coupling of Grignard reagents with 5-alkyl-2,3-dihydrofurans first reported by Wenkert and co-workers[1] is an efficient and highly stereoselective method for making tri-substituted double bonds. The reaction can be run on a substantial scale and makes use of cheap, readily available catalysts. The reaction should provide a valuable alternative to recent methods based on carboalumination[4] and carbocupration[5] of terminal acetylenes for the synthesis of homoallylic alcohols which are valuable intermediates for the synthesis of terpenoids and other natural products.

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