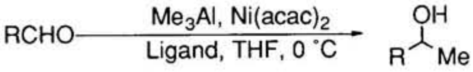
Acceleration Effects of Phosphine Ligands in the Nickel Catalyzed Methylation of Aldehydes Using Trimethylaluminum

Tsuyoshi Ichiyanagi, Satoru Kuniyama, Makoto Shimizu, and Tamotsu Fujisawa*
Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507

(Received July 17, 1998; CL-980526)

A nickel catalyzed methylation of aldehydes was conducted successfully using trimethylaluminum as an alkylation reagent. In the presence of a phosphine or phosphite ligand, the reaction was considerably accelerated to give the methylation product in good yields.

Ligand accelerated reactions are of interest due to their potential on application to asymmetric synthesis. For example, it is well-known that the presence of β-aminoalcohols accelerates the ethylation with diethylzinc,[1] cinnconalkaloids catalyze the osmiun-mediated asymmetric dihydroxylation,[2] and the enantioselective reduction of ketones or imines is effected by oxazaborolidines.[3] From the standpoint of chemoselectivity, organoaluminums have distinctive features as compared with organolithiums, Grignard reagents,[4] or organocuprates.[5] We have been interested in the reactivity of organoaluminums and recently reported that trialkylaluminum worked as a good carbon nucleophile in the nickel catalyzed regioselective ring-opening of cyclopropyl ketones.[6] In general, for the methylation of ketones and aldehydes with trimethylaluminum as a methylating reagent, hexane or toluene, a non-polar solvent, is used. However, almost no methylation product is obtained by the use of a polar solvent such as THF.[7] In the present study, a nickel catalyzed methylation of aldehydes using trimethylaluminum as a carbon nucleophile was examined, and we have found that the addition of a phosphine ligand improved the reactivity of the reagent and considerably increased the product yield.



General procedure for the nickel catalyzed methylation of benzaldehyde with trimethylaluminum is as follows: To a solution of nickel acetylacetonate (6.4 mg 0.025 mmol) in THF (2.0 ml) was added a solution of the ligand (0.05 mmol) and the aldehyde (0.5 mmol) in THF (3.0 ml) at 0 °C under argon. After stirring for 10 min, a solution of trimethylaluminum (0.98 M in hexane, 1.0 mmol) was added to the mixture at the same temperature, and the reaction was monitored by TLC. The reaction mixture was quenched by the addition of 2M HCl, extracted with diethyl ether, and then washed with brine. The combined organic layers were dried over sodium sulfate and concentrated in vacuo, and the crude product was purified on silica-gel thin layer chromatography to give 1-phenylethanol. Table 1 shows the effect of the ligand on the nickel catalyzed methylation of benzaldehyde in THF at 0 °C.

Table 1. Ligand effect on the methylation of benzaldehyde with trimethylaluminum catalyzed by nickel acetylacetonate

Entry	$Ni(acac)_2$ / mol%	Ligand / mol%	Time / h	Yield / %[a]
1	none	none	48	N.R.
2	5	none	3	33
3	5	PPh_3 / 10	1	83
4	5	$n\mathrm{Bu}_3P$ / 10	2	74
5	10	$(PhO)_3P$ / 20	1	72
6	5	$(EtO)_3P$ / 10	0.5	83
7	5	dppe[b] / 10	0.5	70
8	5	dppb[c] / 10	5	71
9	5	TMEDA[d] / 5	3	33
10	5	Bipy[e] / 5	21	38
11	0.5	PPh_3 / 1.0	1	87
12	0.1	PPh_3 / 0.2	26	81
13	0.01	PPh_3 / 0.02	38	19

[a] Isolated yield. [b] Diphenylphosphinoethane. [c] Diphenylphosphinobutane. [d] *N,N,N',N'*-Tetraethylethylenediamine. [e] 2,2'-Bipyridil.

Benzaldehyde did not react with trimethylaluminum in THF at room temperature (entry 1). Although the addition of 5 mol% of nickel acetylacetonate effected the methylation to give 1-phenylethanol, it was obtained in 31% with low conversion yield even after 8 h (entry 2). When triphenylphosphine was added as a ligand, the reaction time was reduced to an hour, and the yield of the methylated product increased up to 83% (entry 3). The use of trialkylphosphines, triarylphosphites, and trialkylphosphites, or the bidentate phosphines such as diphenylphosphinoethane and diphenylphosphinobutane gave essentially the same results (entries 4, 5, 6, 7, and 8). No acceleration effect was observed when amines were used as ligands. (entries 9 and 10). The amount of nickel could be reduced to as low as 0.5 mol% under the same conditions (entry 11). However, the use of 0.1 mol% of the catalyst resulted in the longer reaction time for completion (entry 12).

As an alkylating reagent, dimethylaluminum chloride or methylaluminum dichloride did not react with benzaldehyde even at 65 °C. The methylated product was obtained in 43% yield when dimethylaluminum 1-phenylethoxide was used instead of trimethylaluminum, in which a longer reaction time was needed. Changing the aluminum reagent to triehyl- and triisobutylaluminum from trimethylaluminum also gave the corresponding alkylated products in good yields but a small amount of benzyl alcohol was formed as a side product presumably via the reduction with β-hydride of the organoaluminum.

Table 2 shows the nickel catalyzed methylation of several aldehydes in THF at 0 °C. All the aliphatic and aromatic aldehydes studied here were methylated with trimethylaluminum in good yields. Effect of the substituent at the aromatic ring was also examined. The use of *p*-anisaldehyde having an electron-donating group increased the product yield, and the reaction was completed within half an hour (entry 7). However, a long reaction time was needed, when *p*-chloro- or *p*-bromobenzaldehyde having an electron-withdrawing group was used. These observations may stem from the enhanced coordination ability of *p*-anisaldehyde with trimethylaluminum as

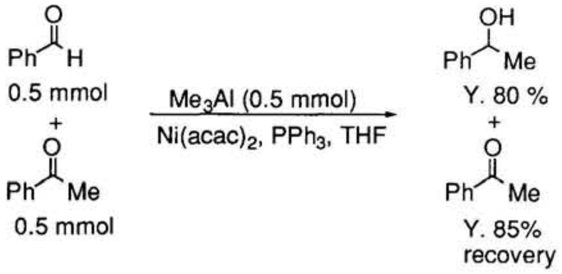
Table 2. The reaction of aldehydes with trimethylaluminum promoted by nickel acetylacetonate[a]

Entry	Aldehyde	Time / h	Yield / %[b]
1	PhCHO	1	83
2	*trans*-PhCH=CHCHO	3	83
3	$PhCH_2CH_2CHO$	3	81
4	*n*-$C_8H_{17}CHO$	2	82
5	*c*-$C_6H_{11}CHO$	11	76
6	2-FurylCHO	0.5	48
7	4-$MeOC_6H_4CHO$	0.5	91
8	4-ClC_6H_4CHO	13.5	91
9	4-BrC_6H_4CHO	21	92
10	2-$MeOC_6H_4CHO$	1	90
11	2,6-$Cl_2C_6H_3CHO$	38	87

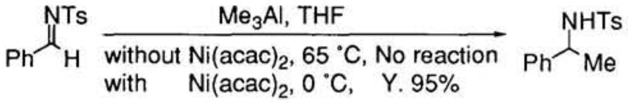
[a]The reaction was carried out according to the typical experimental procedure in the text. [b]Isolated yield.

compared with *p*-haloaldehydes due to the electronic effect of the substituent.

The present system has high chemoselectivity. The reaction of a mixture of benzaldehyde and acetophenone with trimethylaluminum catalyzed by nickel gave 1-phenylethanol in 80% yield and acetophenone was recovered. The methylation of acetophenone, *N*-benzylbenzalimine, or methyl benzoate at 0 °C under the typical conditions did not give the methylated product.



Although an activated imine, *N*-tosylbenzalimine, could not react with trimethylaluminum in the absence of nickel species, the addition of the catalyst gave 1-phenyl-1-(*p*-toluenesulfonyl)-aminoethane in good yield.



The mechanism of the present nickel catalyzed methylation of aldehydes may be explained as follows: the reaction of nickel acetylacetonate and trimethylaluminum produces dimethylnickel species,[8] and it appears to be the true methylation reagent in the present system. An excess trimethylaluminum activates the aldehyde due to the coordination to the carbonyl oxygen, and then the aldehyde reacts with the dimethylnickel to give the methylated product. When the phosphine ligand is added to this system, dimethylnickel is smoothly generated due to the stabilization effect by the phosphine ligand with suppressing the reduction of nickel (II) to nickel (0) species, and therefore, the reaction is accelerated with the increased product yield. The difference of the reactivity of the substituted aldehydes may be explained in terms of the coordination ability of the aldehydes.

In conclusion, the nickel catalyzed methylation of aldehydes using trimethylaluminum was promoted in the presence of phosphine ligands, resulting in the increase in product yields. This system may be extended to the asymmetric version and used as a chemoselective method for C-C bond formations.

References and Notes

1 a) N. Oguni and T. Omi, *Tetrahedron Lett.*, **25**, 2823 (1984). b) R. Noyori, M. Kitamura, S. Suga, and K. Kawai, *J. Am. Chem. Soc.*, **108**, 6071 (1986).
2 H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, **94**, 2483 (1994).
3 a) A Hirao, S. Itsuno, S. Nakahama, and Y. Yamazaki, *J. Chem. Soc., Chem. Commun.*, **1981**, 315. b) E. J. Corey, R. K. Bakshi, and S. Shibuya, *J. Am. Chem. Soc.*, **109**, 5551 (1987). c) M. Shimizu, M. Kamei, and T. Fujisawa, *Tetrahedron Lett.*, **36**, 8607 (1995).
4 a) J. P. Kennedy, *J. Org. Chem.*, **35**, 532 (1970). b) D. W. Harry, A. Meisters, and T. Mole, *Aust. J. Chem.*, **27**, 1665 (1974). c) A. Meisters and T. Mole, *Aust. J. Chem.*, **27**, 1655 (1974).
5 a) L. Bagnell, E. A. Jeffery, A. Meisters, and T. Mole, *Aust. J. Chem.*, **28**, 801 (1975). b) R. T. Hansen, D. B. Car, and J. Schwartz, *J. Am. Chem. Soc.*, **100**, 2244 (1978).
6 T. Ichiyanagi, S. Kuniyama, M. Shimizu, and T. Fujisawa, *Chem. Lett.*, **1997**, 1149.
7 a) E. C. Ashby and T. Laemmle, *J. Org. Chem.*, **40**, 1469 (1975). b) E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, **37**, 1918 (1972).
8 a) T. Yamamoto, M. Takamatsu, and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, **55**, 325 (1982). b) A. Yamamoto, T. Yamamoto, and F. Ozawa, *J. Synth. Org. Jpn.*, **41**, 827 (1983). c) T. Yamamoto, T. Kohara, and A. Yamamoto, *Chem. Lett.*,**1976**, 1217.