VIP Asymmetric Catalysis

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Catalytic Asymmetric Alkylation of Aldehydes with Grignard Reagents**

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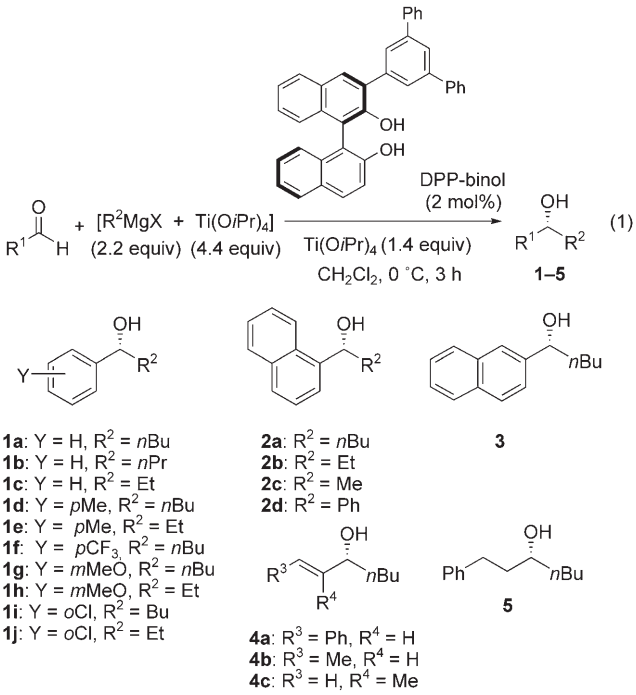
The catalytic asymmetric addition of organometallic reagents to carbonyl compounds is a reaction of fundamental importance in modern synthetic organic chemistry.[1] Less reactive reagents, typically diorganozinc derivatives,[2,3] are used to achieve this transformation because a direct, noncatalyzed reaction would deminish the enantioselectivity.[4–6] The reaction of Grignard reagents with carbonyl compounds is one of the most reliable methods for forming carbon–carbon bonds. However, Grignard reagents have been recognized to be unsuitable for asymmetric alkylation, because to their high reactivity. Indeed, in previously reported asymmetric alkylations with Grignard reagents, more than a stoichiometric amount of a chiral modifier was required to obtain high enantioselectivity.[7] A taddolate–titanium(IV)-catalyzed reaction (taddol = α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) of dialkylzinc derivatives, generated in situ from Grignard reagents and $ZnCl_2$ with strict exclusion of magnesium salts, have also been reported.[8,9]

We recently reported[10] that a titanium(IV) complex derived from (*R*)-3-(3,5-diphenylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (DPP-binol) exhibits a remarkably enhanced catalytic activity in the asymmetric alkylation of aldehydes with diethylzinc.[11,12] This observation prompted us to examine the catalyst derived from DPP-binol in the reaction with Grignard reagents. Herein, we report that the asymmetric alkylation of aldehydes can be achieved by using Grignard reagents in the presence of a catalytic amount of DPP-binol (2 mol%) and excess titanium tetraisopropoxide [Eq. (1)].



The general procedure is straightforward: A Grignard reagent (R^2MgX; X = Cl, Br, 2–3 M in Et_2O or THF; 2.2 equiv) is treated with titanium tetraisopropoxide (4.4 equiv) in CH_2Cl_2 at −78 °C. The resulting mixture, containing titanate $[R^2Ti(OiPr)_4]MgX$,[13] is slowly added (over a period of 2 h) to a solution of an aldehyde, (*R*)-DPP-binol (2 mol%), and titanium tetraisopropoxide (1.4 equiv) in CH_2Cl_2 at 0 °C and is stirred for a further 1 h. Subsequent aqueous workup followed by Kugelrohr distillation or flash chromatography on silica gel then affords the corresponding secondary (*R*)-alcohol (**1**–**5**) enantioselectively.

Results for the asymmetric alkylation of various aldehydes using Grignard reagents are summarized in Table 1. The reaction of aromatic aldehydes, including 1- and 2-naphthaldehyde, with *n*BuMgCl afforded the corresponding butylation products in high yield and enantioselectivity (91–96% *ee*; Table 1, entries 1, 6, 8, 9, 11, 13, and 19). The reactions with *n*PrMgCl (entry 4) and EtMgX (X = Cl, Br) were also enantioselective (entries 5, 7, 10, 12, 14, and 16), whereas the yield of the ethylation products was moderate (see below). Chloromagnesium reagents and bromomagnesium reagents could be employed with comparable efficiency and selectivity (entries 14 and 16). The solvent in which the Grignard reagents are prepared influences the reaction outcome. EtMgCl in Et_2O gave better enantioselectivity compared with THF (compare entries 14 and 15). The use of unsubstituted binol in the reaction of benzaldehyde with *n*BuMgCl resulted in decreased enantioselectivity (79% *ee*) and yield (77%) of the butylation product (entry 3).

The reaction of 1-naphthaldehyde with MeMgCl resulted in low enantioselectivity (entry 17). In contrast, relatively high enantioselectivity was obtained for the phenylation with PhMgBr (entry 18). Aromatic aldehydes as well as α,β-unsaturated aldehydes reacted efficiently with *n*BuMgCl

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Table 1: Catalytic asymmetric alkylation of aldehydes with Grignard reagents.[a]

Entry	Aldehyde	RMgX[b]	Alkylation product	Yield [%][c]	*ee* [%]
1	PhCHO	*n*BuMgCl	**1a**	86	93
2[d]	PhCHO	*n*BuMgCl	**1a**	94	92
3[e]	PhCHO	*n*BuMgCl	**1a**	77	79
4	PhCHO	*n*PrMgCl	**1b**	82	94
5	PhCHO	EtMgCl	**1c**	57	90
6	*p*-MeC_6H_4CHO	*n*BuMgCl	**1d**	82	95
7	*p*-MeC_6H_4CHO	EtMgCl	**1e**	41	88
8	*p*-$CF_3C_6H_4CHO$	*n*BuMgCl	**1f**	62	95
9	*m*-$MeOC_6H_4CHO$	*n*BuMgCl	**1g**	86	95
10	*m*-$MeOC_6H_4CHO$	EtMgCl	**1h**	40	95
11	*o*-ClC_6H_4CHO	*n*BuMgCl	**1i**	79	94
12	*o*-ClC_6H_4CHO	EtMgCl	**1j**	46	80
13	1-naphCHO	*n*BuMgCl	**2a**	90	96
14	1-naphCHO	EtMgCl	**2b**	56	94
15	1-naphCHO	EtMgCl[f]	**2b**	39	84
16	1-naphCHO	EtMgBr	**2b**	63	93
17	1-naphCHO	MeMgCl[f]	**2c**	89	28
18	1-naphCHO	PhMgBr	**2d**	94	86
19	2-naphCHO	*n*BuMgCl	**3**	92	91
20	PhCH=CHCHO	*n*BuMgCl	**4a**	60	91
21	CH_2=C(CH_3)CHO	*n*BuMgCl	**4b**	49	84
22	$PhCH_2CH_2CHO$	EtMgCl	**5**	36	92

[a] Unless otherwise noted, reactions were carried out on a 1-mmol scale with DPP-binol (2 mol%) according to the procedure described in the Experimental Section. [b] Unless otherwise noted, a commercial solution in Et_2O (1.6–3 M) was used. [c] Yields of isolated product. [d] The reaction was performed on a 10-mmol scale. [e] Binol (2 mol%) was used. [f] THF solution. naph = naphthalene.

to give the corresponding allylic alcohols **4a** and **4b** enantioselectively (entries 20 and 21). Although sluggish, the reaction of an aliphatic aldehyde was also enantioselective (entry 22).

The pinacol coupling of aldehydes was observed as a major side reaction when using the alkyl Grignard reagents.[14,15] In the ethylation reaction, the corresponding pinacol by-product ($R^1CH(OH)CH(OH)R^1$) was formed in 22–44% yield. The side reaction was less dominant for *n*PrMgCl and *n*BuMgCl (<10%) and not observed for MeMgCl and PhMgX (X = Cl, Br).

To demonstrate the preparative utility of our asymmetric alkylation procedure, the reaction of benzaldehyde with *n*BuMgCl was carried out on a 10.5-mmol scale. Kugelrohr distillation of the crude product gave **1a** (1.62 g, 94% yield) in 92% *ee* (entry 2), and DPP-binol was recovered quantitatively by flash chromatography of the distillation residue.

In summary, we have demonstrated that Grignard reagents can be effective in asymmetric alkylation of aldehydes by using a catalyst derived from binol–titanium(IV) derivative in the presence of excess titanium tetraisopropoxide. The reaction proceeds with a low catalyst loading (2 mol%) and exhibits high enantioselectivity for aromatic and unsaturated aldehydes as well as for both alkyl and aryl Grignard reagents.

Experimental Section

Typical procedure: (*R*)-1-Phenylpentan-1-ol (**1a**; Table 1, entries 1 and 2): *n*BuMgCl (2 M in Et_2O; 1.10 mL, 2.2 mmol) was added to a solution of titanium tetraisopropoxide (1.30 mL, 4.4 mmol) in dry CH_2Cl_2 (16 mL) at −78 °C in an argon atmosphere. After stirring the reaction for 10 min at this temperature, it was slowly added (over a period of 2 h by using a syringe pump) to a solution of (*R*)-DPP-binol (10.3 mg, 0.020 mmol), benzaldehyde (0.106 g, 1.0 mmol), and titanium tetraisopropoxide (0.41 mL, 1.4 mmol) in CH_2Cl_2 (4 mL) at 0 °C in an argon atmosphere and stirred for a further 1 h. The reaction mixture was then quenched by the addition of aqueous 1N HCl and extracted three times with Et_2O. The organic layers were washed successively with aqueous 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Kugelrohr distillation (150 °C/5 mm Hg) gave **1a** (0.141 g, 86% yield, 93% *ee*). The distillation residue was purified by flash chromatography on silica gel (10–50% ethyl acetate in *n*-hexane) and gave (*R*)-DPP-binol (6.1 mg, 59% recovery) and 1,2-diphenylethane-1,2-diol (4.2 mg, 4% yield), where *meso*:*dl* = 1.3:1. The *ee* value was determined by HPLC analysis using a Chiralcel OD column (1.0 mL min^{-1}, 2% *i*PrOH in *n*-hexane); retention times: 11.8 min (major *R* enantiomer) and 14.7 min (minor *S* enantiomer). The absolute configuration of the product was determined based on the reported retention times:[16] 12.9 min (*R* enantiomer) and 16.4 min (*S* enantiomer).

The above reaction was repeated on a 10.5-mmol scale by following the same procedure except that a dropping funnel was used for the slow addition over 2 h. Kugelrohr distillation (120–150 °C/5 mm Hg) of the crude products gave (*R*)-**1a** (1.62 g, 94% yield, 92% *ee*) ($[\alpha]_D^{25} = 35.4\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.0303\ g\,cm^{-3}$, C_6H_6)). The distillation residue was purified by flash chromatography on silica gel (10–50% ethyl acetate in hexane) to give (*R*)-DPP-binol (101.2 mg, 98% recovery) and 1,2-diphenylethane-1,2-diol (76.2 mg, 7% yield), where *meso*:*dl* = 1.4:1.

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