DOI: 10.1002/ejoc.201101283

Catalytic Enantioselective Addition of MeMgBr and Other Grignard Reagents to Aldehydes

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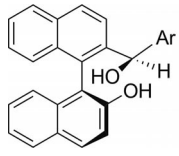
Dedicated to Professor Dr. Carmen Nájera on the occasion of her 60th birthday

Keywords: Asymmetric catalysis / Grignard reaction / Aldehydes / Alcohols / Titanium

Herein, we report an efficient catalyst for the challenging enantioselective addition of MeMgBr to aldehydes. Unprecedented yields and enantioselectivities are achieved in the reaction with a broad range of aldehydes. Moreover, a variety of Grignard reagents can be also added to aromatic and aliphatic aldehydes in good yields and enantioselectivities in a simple one-pot procedure under mild conditions.

Introduction

The chiral methyl carbinol moiety is present in a large number of natural products and biologically active compounds,[1] and its synthesis is of great importance to both academia and industry. One of the most efficient approaches to this structural fragment is the catalytic asymmetric addition of a methyl group to an aldehyde, which involves the formation of both a new C–C bond and the corresponding stereogenic center.[2] Enantioselective catalyzed versions of this key transformation have been studied extensively with dimethylzinc[3,4] and trimethylaluminum.[5] However, for the highly reactive methyllithium and methyl Grignard reagents, the progress has been limited[6] and more than stoichiometric amounts of a chiral modifier are usually required to obtain good enantioselectivity.[7] As an alternative, methyl Grignard reagents can be transmetalated into dimethylzinc[8] or methyltitanium triisopropoxide[9] and, after tedious removal of the generated magnesium salts, used in asymmetric additions to aldehydes. Recently, two notable examples of the highly enantioselective catalytic addition of Grignard reagents to aldehydes have been reported by Harada[10] and later by Da.[11] Both approaches comprise the use of an excess amount of titanium(IV) isopropoxide and no salt exclusion is needed to achieve high enantioselectivities. Nevertheless, none of these systems seems to be effective for the addition of methyl Grignard reagents, and very low enantioselectivities are obtained with the use of a high catalyst loading (40 mol-%).[11] Here, we report a facile one-pot methodology for the addition of MeMgBr to different aldehydes by using an excess amount of titanium tetraisopropoxide in the presence of a catalytic amount of the readily available chiral ligand (S_a,*R*)-**L1** (Figure 1).[12] This methodology provides the highest enantioselectivities and yields reported so far for this process. Moreover, enantioselective alkylation of a wide variety of aldehydes by using other longer-chain Grignard reagents proved to be also effective with this catalytic system.



(S_a,*R*)-**L1**: Ar = Ph
(S_a,*S*)-**L2**: Ar = *o*-MeOC$_6$H$_4$
(S_a,*R*)-**L3**: Ar = *m*-MeOC$_6$H$_4$
(S_a,*R*)-**L4**: Ar = *p*-MeOC$_6$H$_4$
(S_a,*R*)-**L5**: Ar = *p*-FC$_6$H$_4$

Figure 1. Chiral ligands used in this study.

Results and Discussion

The recently published straightforward synthesis of 1,1′-binaphthalene-2-α-arylmethan-2′-ols (Ar-BINMOLs) by Lai and Xu[12] encouraged us to analyze these kinds of binaphthyl-based chiral diols as ligands in the enantioselective addition of Grignard reagents to carbonyl compounds.

As a model reaction for this study, we chose the addition of MeMgBr to *o*-methylbenzaldehyde (**1a**) or benzaldehyde (**1b**). The first promising results were achieved with 10 mol-% of ligand (S_a,*R*)-**L1**, which provided 20 and 35%*ee* and full conversion in the addition of MeMgBr to **1a** at 0 °C with the use of toluene or diethyl ether, respectively, as solvent (Table 1, Entries 1 & 2). Other solvents like DCM, THF, and *t*BuOMe were evaluated, but the enantio-

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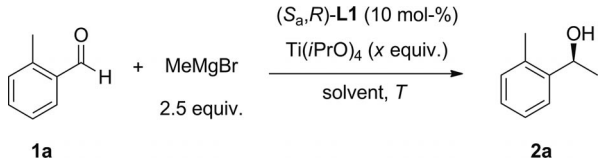
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101283.

selectivities were lower in all cases (Table 1, Entries 3–5). The effect of the temperature was then analyzed. Lowering the temperature to –20 °C produced a drastic decrease in both conversion and enantioselectivity when the reaction was carried out in diethyl ether (Table 1, Entry 6), probably due to solubility problems.[13] Fortunately, the use of toluene at –40 °C provided an increase in the enantioselectivity up to 51% (Table 1, Entry 7), preserving the full conversion of **1a** into **2a**. Lower temperatures (–60 °C) led to a significant decrease in the rate of the reaction (60% conversion; Table 1, Entry 8), although the enantioselectivity was found to be higher (54%).

Table 1. Addition of MeMgBr to *o*-methylbenzaldehyde.[a]



1a **2a**

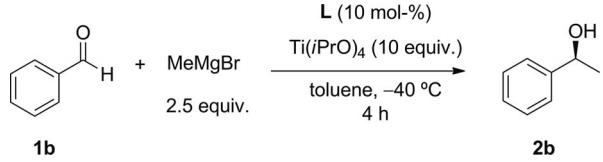
Entry	*T* [°C]	Solvent	Ti(*i*PrO)$_4$ [equiv.]	Conv. [%][b]	*ee* [%][c]
1	0	toluene	10	99	20
2	0	Et_2O	10	98	35
3	0	DCM	10	99	16
4	0	THF	10	70	8
5	0	*t*BuOMe	10	99	0
6	–20	Et_2O	10	20	5
7	–40	toluene	10	99	51
8	–60	toluene	10	60	54
9	–40	toluene	0	90	0
10	–40	toluene	2.5	99	0
11	–40	toluene	5	89	30
12	–40	toluene	7.5	90	44
13	–40	toluene	12.5	90	40

[a] Conditions: **1a** (1 equiv., 0.07 M), MeMgBr (3 M in Et_2O, 2.5 equiv.), (S_a,*R*)-**L1** (10 mol-%), Ti(*i*PrO)$_4$ (*x* equiv.), 4 h. [b] Determined by GC. [c] Determined by chiral HPLC (see the Supporting Information for details).

The amount of titanium tetraisopropoxide was crucial to the process and low loadings led to a drastic decrease in the enantioselectivity (Table 1, Entries 7, 9–13). We believe that a large excess of the Lewis acid Ti(*i*PrO)$_4$ is needed to prevent the complexation of the magnesium salts (produced during the transmetalation process and responsible for the uncatalyzed reaction)[10] to the carbonyl moiety. In view of these results, we concluded that 4 equiv. of Ti(*i*PrO)$_4$ with respect to MeMgBr (Table 1, Entry 7) was the optimal amount to achieve the highest enantioselectivity.

With these preliminary conditions, we decided to screen a small library of Ar-BINMOLs (Figure 1 and Table 2) as ligands for the addition of MeMgBr to benzaldehyde (**1b**). The corresponding diastereomer of (S_a,*R*)-**L1**, with same axial chirality but opposite configuration at the sp^3 center, was synthesized by treatment of (S_a,*R*)-**L1** with 6 M HCl in THF at room temperature (20% yield, see the Supporting Information for details). However, new ligand (S_a,*S*)-**L1** provided no enantioselectivity in the alkylation reaction with benzaldehyde (Table 2, Entry 2). Methoxy-substituted Ar-BINMOLs [(S_a,*S*)-**L2**, (S_a,*R*)-**L3**, and (S_a,*R*)-**L4**] gave lower enantioselectivities (Table 2, Entries 3–5) than simpler phenyl-BINMOL (S_a,*R*)-**L1** (Table 2, Entry 1). Moreover, lower conversion was observed in the case of *meta*-methoxy-substituted (S_a,*R*)-**L3**. *para*-Fluoro-substituted ligand (S_a,*R*)-**L5** proved equally effective as (S_a,*R*)-**L1** (Table 2, Entry 6), although it was less stable at ambient conditions.[14]

Table 2. Asymmetric addition of MeMgBr to benzaldehyde: screening of ligands.[a]



1b **2b**

Entry	Ar in **L**	**L**	Conv. [%][b]	*ee* [%][b]
1	Ph	(S_a,*R*)-**L1**	90	80
2	Ph	(S_a,*S*)-**L1**	71	0
3	*o*-$MeOC_6H_4$	(S_a,*S*)-**L2**	86	48
4	*m*-$MeOC_6H_4$	(S_a,*R*)-**L3**	25	74
5	*p*-$MeOC_6H_4$	(S_a,*R*)-**L4**	89	70
6	*p*-FC_6H_4	(S_a,*R*)-**L5**	89	83

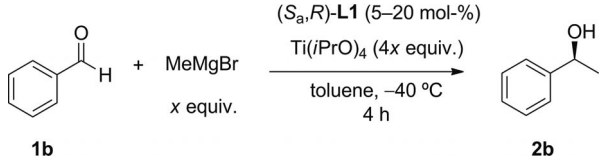
[a] Conditions: **1b** (1 equiv., 0.07 M), MeMgBr (3 M in Et_2O, 2.5 equiv.), **L** (10 mol-%), Ti(*i*PrO)$_4$ (10 equiv.), toluene, –40 °C, 4 h. [b] Determined by chiral GC (see the Supporting Information for details).

Different additives such as dioxane, crown ethers, bis[2-(*N*,*N*-dimethylamino)ethyl] ether (BDMAEE),[11] molecular sieves, and so on were tested without any improvement in the enantioselectivity. A wide variety of titanium sources [e.g., Ti(OMe)$_4$, Ti(OEt)$_4$, Ti(*n*PrO)$_4$, Ti(*t*BuO)$_4$] were also used, but very low conversions and enantioselectivities were obtained in all cases (see the Supporting Information for further details).

In a last effort to improve our methodology, we examined the influence of the catalyst loading and amount of MeMgBr in the reaction with benzaldehyde (**1b**, Table 3). Higher ligand loadings improved both the conversion and enantioselectivity of the reaction (Table 3, Entries 1–3) up to 79% conversion and 85%*ee* when using 20 mol-% of (S_a,*R*)-**L1** (Table 3, Entry 3). To reach full conversion, the number of equivalents of MeMgBr was increased to 3.75. Under these last adjustments, the enantioselectivity slightly increased up to 88% (Table 3, Entry 4).

With the optimized conditions in hand (Table 3, Entry 4), we studied the addition of MeMgBr to different aldehydes (Table 4). The highly desirable addition of poorly reactive MeMgBr was achieved in high yields with high enantioselectivities (80–90%*ee*) for a wide variety of aromatic aldehydes with electron-poor and electron-rich substituents in the *meta* and *para* positions (Table 4, Entries 1, 3–9). The alkylation of *o*-methylbenzaldehyde proceeded with lower enantioselectivity (53%*ee*; Table 4, Entry 2), probably due to the steric hindrance close to the reactive

Table 3. Asymmetric addition of MeMgBr to benzaldehyde: effect of catalyst loading.[a]



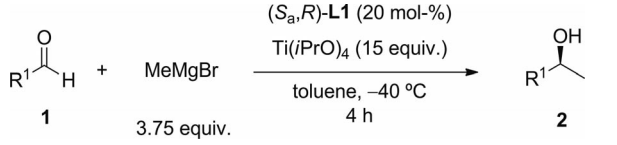
Entry	(S_a,*R*)-**L1** [mol-%]	MeMgBr [equiv.]	Ti(*i*PrO)$_4$ [equiv.]	Conv. [%][b]	*ee* [%][b]
1	5	1.25	5	60	78
2	10	1.25	5	73	83
3	20	1.25	5	79	85
4	20	3.75	15	98	88

[a] Conditions: **1b** (1 equiv., 0.07 M), MeMgBr (3 M in Et_2O, *x* equiv.), (S_a,*R*)-**L1** (5–20 mol-%), Ti(*i*PrO)$_4$ (4*x* equiv.), toluene, –40 °C, 4 h. [b] Determined by chiral GC (see the Supporting Information for details).

site. The reaction with phenylacetaldehyde proceeded with moderated enantioselectivity (68%*ee*) and poor yield (43%) at –40 °C (Table 4, Entry 10); gratifyingly, the yield could be improved to 70% by increasing the temperature to –20 °C without observing any loss in enantioselectivity (Table 4, Entry 11). The use of cinnamaldehyde or 2-thiophenecarboxaldehyde prompted a decrease in the enantioselectivity values (Table 4, Entries 12 & 13). It should be mentioned that full conversion was achieved in almost all the cases and no byproducts were formed under the optimized conditions. Only phenylacetaldehyde did not react completely (probably due to the high acidity of the benzylic hydrogen atoms) and it could be recovered at the end of the reaction (Table 4, Entries 10 & 11). Moreover, ligand (S_a,*R*)-**L1** could also be recovered and recycled without observing any loss in catalytic activity (see the Supporting Information for further details).

Encouraged by the excellent results in the addition of the challenging MeMgBr reagent, we turned our attention to the use of other Grignard reagents (Table 5). The addition of linear Grignard reagents like EtMgBr and *n*BuMgBr proceeded in good yields and with good enantioselectivities (up to 96%*ee*) for a wide range of aromatic aldehydes with electron-donating or electron-withdrawing groups (Table 5, Entries 1–4, 6, and 7). Moreover, *n*BuMgBr could be added at –20 °C to an aliphatic aldehyde with moderated enantioselectivity (50%*ee*; Table 5, Entry 8) and good yield.[15] The use of *n*BuMgCl provided the same enantioselectivity as that of its bromide-derived counterpart; however, the conversion only reached a moderated level and 19% of benzyl alcohol was formed during the reaction (Table 5, Entry 5). Bulky *i*BuMgBr gave an excellent enantioselectivity but poor yield in the reaction with benzaldehyde (96%*ee*, 41% yield; Table 5, Entry 9) and the formation of 5% of benzyl alcohol was detected. An improvement in the yield could be achieved at higher temperatures (–20 °C), but at the expense of the enantioselectivity (Table 5, Entry 10). A limitation of this methodology is the use of secondary *i*PrMgBr,

Table 4. Asymmetric addition of MeMgBr to aldehydes: scope of the reaction.[a]

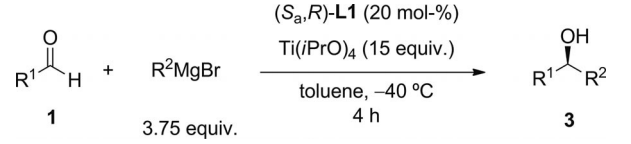


Entry	R^1	Yield [%][b]	*ee* [%][c,d]
1	Ph	92	88 (*S*)
2	*o*-MeC_6H_4	85	53 (*S*)
3	*m*-MeC_6H_4	99	88 (*S*)
4	*p*-Me-C_6H_4	98	87 (*S*)
5	*p*-MeOC_6H_4	95	80 (*S*)
6	*p*-$CF_3C_6H_4$	88	88 (*S*)
7	*p*-ClC_6H_4	98	84 (*S*)
8	*p*-CNC_6H_4	89	85 (*S*)
9	2-naphthyl	92	90 (*S*)
10	Bn	43	68 (*S*)
11[e]	Bn	70	70 (*S*)
12	PhCH=CH	90	68 (*S*)
13	2-thienyl	53[f] (98)[g]	58 (*S*)

[a] Conditions: **1** (1 equiv., 0.12 M), MeMgBr (3 M in Et_2O, 3.8 equiv.), (S_a,*R*)-**L1** (20 mol-%), Ti(*i*PrO)$_4$ (15 equiv.), toluene, –40 °C, 4 h. [b] Isolated yield after flash chromatography. [c] Determined by chiral GC or HPLC (see the Supporting Information for details). [d] Absolute configuration determined by correlation with known compounds (see the Supporting Information). [e] Performed at –20 °C. [f] Volatile product. [g] Yield based on GC data.

which provided a very low conversion to the corresponding racemic alcohol in the reaction with benzaldehyde (Table 5, Entry 11). The addition of the sp^2-hybridized Grignard rea-

Table 5. Asymmetric addition of R^2MgBr to aldehydes: scope of the reaction.[a]



Entry	R^1	R^2	Yield [%][b]	*ee* [%][c,d]
1	Ph	Et	95	86 (*S*)
2	*p*-MeC_6H_4	Et	80	78 (*S*)
3	*p*-ClC_6H_4	Et	85	72 (*S*)
4	Ph	*n*Bu	90	96 (*S*)
5[e,f]	Ph	*n*Bu	41	96 (*S*)
6	*p*-ClC_6H_4	*n*Bu	89	93 (*S*)
7	*p*-MeOC_6H_4	*n*Bu	81	92 (*S*)
8[g]	cyclohexyl	*n*Bu	98	50 (*S*)
9[h]	Ph	*i*Bu	41	96 (*S*)
10[g,h]	Ph	*i*Bu	91	86 (*S*)
11	Ph	*i*Pr	nd (10)[i]	0
12	2-naphthyl	Ph	98 (99)[i]	15 (*R*)

[a] Conditions: **1** (1 equiv., 0.12 M), R^2MgBr (3.8 equiv.), (S_a,*R*)-**L1** (20 mol-%), Ti(*i*PrO)$_4$ (15 equiv.), toluene, –40 °C, 4 h. [b] Isolated yield after flash chromatography. [c] Determined by chiral GC or HPLC (see the Supporting Information for details). [d] Absolute configuration determined by correlation with known compounds (see the Supporting Information). [e] *n*BuMgCl was used instead. [f] 40% of unreacted **1a** and 19% of benzyl alcohol were isolated. [g] Performed at –20 °C. [h] 5% of benzyl alcohol was isolated. [i] Yield based on GC data.

gent PhMgBr to 2-naphthaldehyde proceeded in good yield, but a low enantioselectivity was observed (Table 5, Entry 12).

Conclusions

In conclusion, we have developed an efficient enantioselective catalytic system for the addition of MeMgBr to aldehydes. This methodology allows the preparation of the very versatile optically active methyl carbinol motif in a simple one-pot procedure by using an economical and commercially available source of the methyl group. A readily available binaphthyl derivative is used as a chiral ligand and an excess amount of titanium tetraisopropoxide was found to be crucial to achieve high enantioselectivities. Moreover, the addition of longer-chain Grignard reagents to aromatic and aliphatic aldehydes could be also achieved in high yields and with high enantioselectivities with the here-presented catalytic system. Currently, efforts are directed towards the elucidation of the reaction mechanism.

Experimental Section

General Procedure for the Synthesis of Chiral Alcohols: In a flame-dried Schlenk tube (S_a,*R*)-**L1** (22.6 mg, 0.06 mmol) was dissolved in toluene (2.5 mL) and Ti(*i*PrO)$_4$ (1.33 mL, 15 equiv., 1.5 mmol) was added to the solution at –40 °C. After 5 min, RMgX (3.8 equiv., 0.38 mmol) was added, and the mixture was stirred for 10 min before adding the corresponding aldehyde (0.3 mmol). The reaction mixture was stirred at –40 °C for 4 h and then quenched with H_2O (5 mL) and 2 M HCl (5 mL). The crude was extracted with EtOAc (3 × 10 mL), and the combined organic layers were neutralized with aq. sat. $NaHCO_3$, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by chromatography on silica gel to give desired alcohols **2**.

Supporting Information (see footnote on the first page of this article): Synthetic procedures, screening of the titanium sources, copies of the ^{1}H and ^{13}C NMR spectra, and traces of the GC and HPLC chromatograms.

Acknowledgments

This work was financially supported by the Spanish Ministerio de Ciencia y Tecnología (Projects CTQ2007-65218/BQU and CTQ2011-24151), Consolider Ingenio 2010 (CSD2007-00006), and Generalitat Valenciana (G.V. PROMETEO/2009/039 and FEDER). Medalchemy is thanked for a gift of chemicals.

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[13] The reaction was also carried out in Et_2O/toluene mixtures but no improvement was observed.
[14] We observed partial decomposition of ligand (S_a,*R*)-**L5** after 3 weeks stored at room temperature.
[15] When the reaction was carried out at –40 °C, no conversion was observed.

Received: September 1, 2011
Published Online: October 20, 2011

