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Catalytic Asymmetric Addition of Organolithium Reagents to Aldehydes

M. Veguillas,[a] R. Solà,[a] L. Shaw[a] and B. Maciá*[a]

Dedicated to the memory of Dr. Michael M. Pollard

Abstract: Herein we report an efficient catalytic system for the titanium promoted enantioselective addition of organolithium reagents to aldehydes, based on chiral Ar-BINMOL ligands. Unprecedented yields and enantioselectivities are achieved in the alkylation reactions of aliphatic aldehydes. Remarkably, methyllithium can be added to a wide variety of aromatic and aliphatic aldehydes, providing versatile chiral methyl carbinol units in a simple one-pot procedure under mild conditions and in very short reaction times.

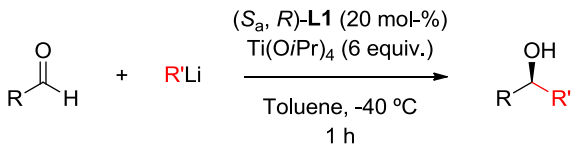
Introduction

Organometallic compounds are amongst the most powerful and versatile reagents in organic synthesis and catalysis.[1] In particular, organolithium reagents are an attractive option in asymmetric synthesis because of their great availability and low cost.[2] However, their application in enantioselective catalysis is challenging due to their high reactivity and strong basicity.[3] These properties often promote uncatalyzed reaction pathways that can lead to loss of chemo-, regio- and enantioselectivity. Few catalytic methods involving organolithium reagents have been described in the literature, focused mainly on asymmetric deprotonation,[4] Br-Li exchange,[5] imine additions,[6] allylic alkylation reactions[7] and alkynalations.[8]

The enantioselective addition of organometallic reagents to carbonyl compounds is a powerful method for the formation of C-C bonds and asymmetric centres in the same synthetic step.[3] Extensive research has been done in this area in the past 20 years, since the asymmetric formation of carbinol motifs – especially those bearing a methyl group – is of great interest in the pharmaceutical industry.[9] In this context, organozinc reagents[10] have found broad application in this field and, more recently, organomagnesium reagents have been employed as well.[11] In the case of organolithium reagents, only few examples have been described, all including the use of very low temperatures and stoichiometric or super stoichiometric amounts of chiral inductors to get high levels of enantioselectivity.[3] In 2011 an example describing substoichiometric use of a chiral ligand was reported by Harrison-Marchand and Maddaluno for the enantioselective addition of methyllithium to *o*-tolylbenzaldehyde.[12]

A common strategy for tempering the high reactivity of alkyllithium reagents is transmetallation into less reactive organometallic species, such as organotitanium reagents. After a strict salt exclusion process, these organotitanium reagents will add to aldehydes in good yields and enantioselectivities in the presence of catalytic amounts of a titanium/TADDOL complex, as reported by Seebach et al, back in 1994.[13a] On a similar note, the transmetallation of aryllithium reagents into their corresponding organozinc[13b] or organomagnesium[13c] compounds allows their catalyzed enantioselective addition to aldehydes, in the presence of *N*,*N*,*N'*,*N'*-tetraethylethylene diamine or an excess of titanium tetraisopropoxide, respectively, to trap the *in situ* generated lithium salts.

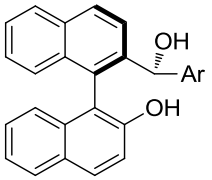
Our research group recently developed an efficient methodology for the catalytic enantioselective addition of organolithium reagents to aldehydes, which allows the direct use of these organometallic species, without the need to perform laborious salt removal procedures.[14] In the presence of catalytic amounts of the (S_a,*R*)-Ph-BINMOL ligand **L1** (Figure 1)[15] and an excess of Ti(O*i*Pr)$_4$, the methodology provides good yields and enantioselectivities for the alkylation of a wide range of aromatic aldehydes. For aliphatic aldehydes, however, lower conversions were observed (probably due to their higher enolisable character) along with lower enantioselectivity (Scheme 1).



R = aryl, R' = alkyl; 19 examples (62-91% yield, 62-96% ee)
R = alkyl; R' = alkyl; 1 example (23% yield, 62% ee)
R = C=C; R' = alkyl; 1 example (84% yield, 68% ee)

Scheme 1. Titanium promoted enantioselective addition of organolithium reagents to aldehydes catalysed by Ph-BINMOL **L1**.

Herein, we describe our efforts towards a more general, efficient and versatile methodology for the enantioselective addition of organolithium reagents to aldehydes, based on Ar-BINMOL ligands and TiCl(O*i*Pr)$_3$. This alternative titanium source allows a substantial reduction in the required loading of titanium and can be used at higher industrially relevant temperatures. Moreover, the substrate scope of the catalytic system here presented includes aliphatic aldehydes.



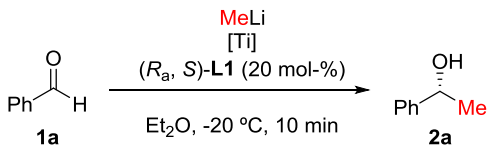
Ar = Ph, (R_a,*S*)-Ph-BINMOL (**L1**)
Ar = 4-Py (R_a,*S*)-4-Py-BINMOL (**L2**)

Figure 1. Ar-BINMOL ligands used in this study.

Results and Discussion

The prevalence of biologically active methyl carbinols prompted us to begin our study using the addition of MeLi to benzaldehyde as model reaction. As previously reported,[14] Ph-BINMOL ligand **L1** catalyses the reaction in the presence of 6 equiv. of Ti(O*i*Pr)$_4$ at –40 °C in toluene, providing 1-phenylethanol (**2a**) in 87% yield and 90% *ee*. We rationalized that a more labile chloride ligand in the titanium source, compared to isopropoxide ligand, could facilitate the process and allow both a reduction of the titanium loading and an increase in the optimal temperature for enantioselective reaction. However, the addition of MeLi to benzaldehyde in the presence of 6.0 equiv. of TiCl(O*i*Pr)$_3$ at –40 °C in toluene, provided 1-phenylethanol (**2a**) in moderate yield (72%) and low enantioselectivity (22% *ee*, entry 1, Table 1). We suspected the low enantioselectivity was due to the racemic addition pathway being promoted by the high excess of titanium salt and, after reducing the charge of titanium salt to 3.2 equiv., we were pleased to obtain alcohol **2a** with good conversion and enantioselectivity (98% conv., 92% *ee*, entry 2, Table 3). In fact, the amount of TiCl(O*i*Pr)$_3$ could be reduced down to 2.5 equiv. without observing any erosion in the enantioselectivity (entry 3, Table 4). Other solvents and temperatures were also tested. While the reaction in THF did not proceed even at higher temperatures (–20 ºC, entry 4, Table 1), the use of Et$_2$O at –20 ºC provided the desired product **2a** with 99% conversion and 70% *ee* (entry 5, Table 1). In search of optimal conditions for a –20 ºC working temperature, we lowered the loading of TiCl(O*i*Pr)$_3$ to 2.0 equiv. (entry 6, Table 1) but, unfortunately, reduced conversion and enantioselectivity were obtained. Full conversion could be restored along with 78% *ee* after adjusting the equivalents of MeLi to 2.0 equiv. (entry 7, Table 1).

Table 1. Optimization of reaction conditions for the addition of MeLi to benzaldehyde.[a]



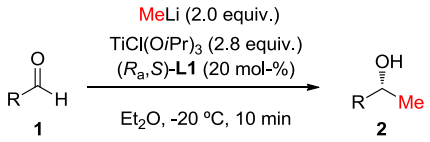
Entry	[Ti] source (equiv.)	MeLi (equiv.)	Conv.[b] [%]	*ee* [%][b] [%]
1[c]	TiCl(O*i*Pr)$_3$ (6.0)	3.2	72	22
2[c]	TiCl(O*i*Pr)$_3$ (3.2)	3.2	98	92
3[c]	TiCl(O*i*Pr)$_3$ (2.5)	3.2	92	92
4[d]	TiCl(O*i*Pr)$_3$ (2.5)	3.2	0	n.d.
5	TiCl(O*i*Pr)$_3$ (2.5)	3.2	99	70
6	TiCl(O*i*Pr)$_3$ (2.0)	3.2	89	30
7	TiCl(O*i*Pr)$_3$ (2.0)	2.0	99	78
8	TiBr$_2$(O*i*Pr)$_2$ (2.5)	3.2	99	0
9	TiF$_4$ (2.5)	3.2	98	0
10	TiCl(O*i*Pr)$_3$ (2.5)	2.0	99	86
11	TiCl(O*i*Pr)$_3$ (2.6)	2.0	98	84
12	**TiCl(O*i*Pr)$_3$ (2.8)**	**2.0**	**99 (90)[e]**	**93**
13	TiCl(O*i*Pr)$_3$ (2.8)	1.7	92	78

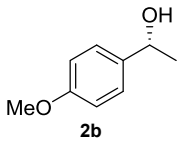
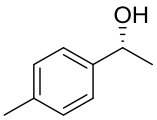
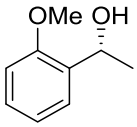
[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv.), MeLi (1.6 M in Et$_2$O), [Ti], (R_a, *S*)-**L1** (0.2 equiv.), Et$_2$O (C = 0.067 M), –20 °C, 10 min. [b] Determined by Chiral GC (see the Supporting Information for details). [c] Performed in toluene at –40 °C, 1 h. [d] Performed in THF at –20 °C, 1 h. [e] Isolated yield after flash chromatography.

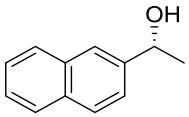
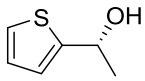
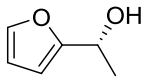
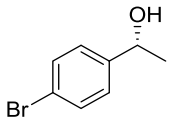
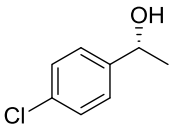
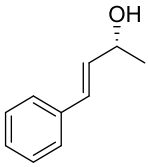
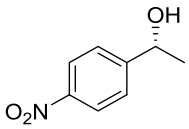
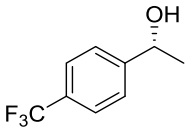
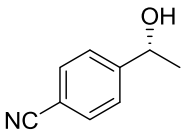
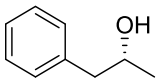
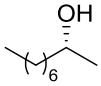
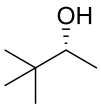
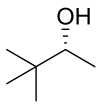
Other titanium sources such as TiBr$_2$(O*i*Pr)$_2$ and TiF$_4$ provided **2a** as a racemic mixture (entries 8 and 9, Table 1). Keeping constant the loading of MeLi at 2.0 equiv., gradual increases in the charge of TiCl(O*i*Pr)$_3$ provided improved enantioselectivities (entries 10-12, Table 1), with the optimal value being 2.8 equiv. (entry 12, Table 1). Further attempts at lowering the equivalents of MeLi were unsuccessful and provided lower enantioselectivity (entry 13, Table 1).

With optimised conditions in hand, the scope of the reaction was then examined, using a number of aldehydes with different substitution patterns and electronic properties (Table 2). Gratifyingly, the catalytic system proved to be both efficient and versatile, promoting the addition reaction in just 10 min with high levels of enantiocontrol in most cases.

Table 2. Asymmetric addition of MeLi to aldehydes using (R_a,*S*)-Ph-BINMOL **L1** as ligand.[a]



Entry	Product	Yield [%][b]	*ee* [%][c]
1	 **2b**	93	92 (*R*)
2	 **2c**	94	90 (*R*)
3		92	44 (*R*)

	2d		
4	 **2e**	85	90 (*R*)
5	 **2f**	95	93 (*R*)
6	 **2g**	(98)[d]	84 (*R*)
7	 **2h**	90	87 (*R*)
8	 **2i**	89	86 (*R*)
9	 **2j**	92	80 (*R*)
10	 **2k**	15 (97)[e]	80 (*R*)
11	 **2l**	92	94 (*R*)
12	 **2m**	93	91 (*R*)
13	 **2n**	80	73 (*R*)
14	 **2o**	94	63 (*R*)[f]
15	 **2p**	(15)[d]	95 (*R*)
16[g]	 **2p**	(20)[d]	89 (*R*)

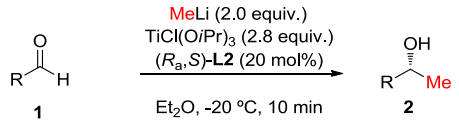
[a] Reaction conditions: aldehyde (0.1 mmol, 1.0 equiv.), MeLi (1.6 M in Et_2O, 2.0 equiv.), (R_a,*S*)-**L1** (0.2 equiv.), $TiCl(O\mathit{i}Pr)_3$ (1.0 M in hexane, 2.8 equiv.), Et_2O, –20 °C, 10 min. [b] Isolated yield after flash chromatography. [c] Determined by Chiral GC. Configuration based on literature data (see Supporting Information for details). [d] Conversion determined by Chiral GC due to the high volatility of the product. [e] Conversion determined by GC due to the product being inseparable from the ligand by flash chromatography. [f] Determined on the corresponding acetate derivative (see Supporting Information for details). [g] Performed at 0 °C.

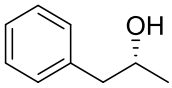
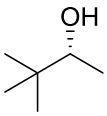
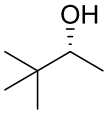
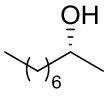
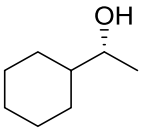
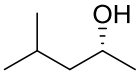
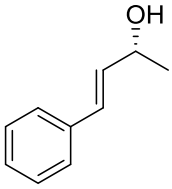
The reaction of MeLi provided high yields and enantioselectivities with the electron rich aromatic aldehydes *p*-anisaldehyde and *p*-tolylaldehyde (entries 1 and 2, Table 2). Unfortunately, lower enantioselectivity was obtained in the addition to *o*-anisaldehyde (44% *ee*, entry 3, Table 2), probably due to steric hindrance close to the reactive site. Other aromatics such as 2-naphthaldehyde and the heteroaromatics 2-thiophen-2-carboxaldehyde and furfural provided high yields and 84-93% *ee* (entries 4-6, Table 2). Bromo- and chloro-substituted aryl aldehydes proved compatible with the reaction conditions and allowed the synthesis of their corresponding carbinols in high yields and enantioselectivities of 87 and 86%, respectively (entries 7 and 8, Table 2). The reaction between *trans*-cinnamaldehyde and MeLi provided the carbinol **2j** in moderate enantiocontrol (80%) and high yield (92%, entry 9, Table 2). Aromatic aldehydes bearing electron-withdrawing substituents (entries 10-12, Table 2) provided high yields (93-97%) and moderate to high enantioselectivities (80-91% *ee*). The compatibility of the catalytic system with labile functionalities such as the cyano group (entry 12) is noteworthy. The more challenging enolizable aliphatic aldehydes provided promising results under these reaction conditions. For example, 2-phenylacetaldehyde gave rise to the corresponding carbinol in 80% yield and 73% *ee* (entry 13, Table 2), while 1-octanal provided higher yield (94%) but lower enantioselectivity (63% *ee*) in the reaction with MeLi (entry 14, Table 2). The non-enolizable but hindered pivaldehyde afforded the corresponding alcohol **2p** with very low conversion (15%, entry 15, Table 2), which could not be rectified by performing the reaction at higher temperatures (0 °C, entry 16, Table 2).

Previous studies in our group showed that 4-Py-BINMOL **L2** exerts higher enantiocontrol than Ph-BINMOL **L1** in the addition of Grignard reagents to aliphatic aldehydes.[16] To our delight, this trend is also observed for the addition of organolithium reagents, in the presence of $TiCl(O\mathit{i}Pr)_3$. Thus, MeLi provided increased enantioselectivity (91% *ee*) and excellent yield (94%, entry 1, Table 3) in the addition to 2-phenylacetaldehyde. Pivaldehyde afforded the desired alcohol **2p** with an excellent 97% *ee* at –20 °C but the reaction conversion was low (28%, entry 2, Table 3). Unfortunately, increasing the temperature of the reaction to 0 ºC did not improve the conversion and the enantioselectivity decreased to 83% *ee* (entry 3, Table 3). The addition of MeLi to octanal gave rise to the corresponding alcohol **2o** in high yield and enantioselectivity (84% yield, 89% *ee*, entry 4, Table 3). The α- and β-branched aliphatic aldehydes such as cyclohexylcarbaldehyde and isopentanal provided alcohols **2q** and **2r**, respectively, in high conversions and enantioselectivities (entries 5 and 6, Table 3). The addition of MeLi to the α,β-unsaturated substrate cynnamaldehyde proceeded with higher

enantiocontrol (90% *ee*) when Py-BINMOL **L2** was used as ligand (entry 7, Table 3) compared to Ph-BINMOL **L1** (80% *ee*, entry 9, Table 2).

Table 3. Asymmetric addition of MeLi to aliphatic aldehydes using (R_a,*S*)-**L2** as ligand.[a]

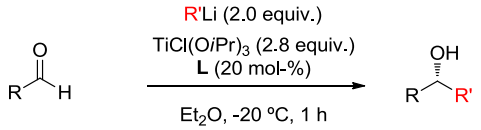


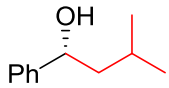
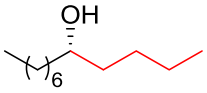
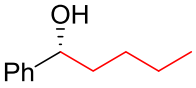
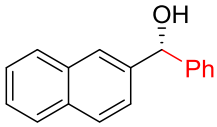
Entry	Product	Yield [%][b]	*ee* [%][c]
1	 **2n**	93	91 (*R*)
2	 **2p**	(28)[d]	97 (*R*)
3[e]	 **2p**	(30)[d]	83 (*R*)
4	 **2o**	84	89 (*R*)[f]
5	 **2q**	(98)[d]	93 (*R*)[f]
6	 **2r**	(87)[d]	94 (*R*)[f]
7	 **2j**	94	90 (*R*)

[a] Reaction conditions: aldehyde (0.1 mmol, 1.0 equiv.), MeLi (1.6 M in Et_2O, 2.0 equiv.), (R_a,*S*)-**L2** (0.2 equiv.), TiCl(O*i*Pr)$_3$ (1.0 M in hexane, 2.8 equiv.) Et_2O, –20 °C, 10 min. [b] Isolated yield by flash chromatography. [c] Determined by chiral GC. Configuration based on literature data (see Supporting Information for details). [d] Conversion determined by chiral GC due to the high volatility of the product. [e] Performed at 0 °C. [f] Determined on the corresponding acetate derivative (see Supporting Information for details).

Upon examining the scope of the reaction with different organolithium reagents (Table 4), we found the addition of *n*-BuLi proceeded with good yields and excellents enantioselectivities with both the aromatic benzaldehyde (after a slight adjustment on the amounts of titanium and organometallic reagent) and the aliphatic octanal (entries 1 and 2, Table 4). The more sterically demanding *i*BuLi, however, provided high yield (91%) in the addition to benzaldehyde but only moderate enantioselectivity (60% *ee*), even after tuning the reaction conditions (entry 3 and footnote c, Table 4). Finally, the aromatic organolithium reagent PhLi, afforded alcohol **6** in good yield (91%) but low enantioselectivity (13% *ee*, entry 4, Table 4).

Table 4. Asymmetric addition of R'Li to aldehydes.[a]



Entry	Product	L	Yield [%][b]	*ee* [%][c]
1[d]	 **3**	**L1**	87	96 (*R*)
2	 **4**	**L2**	78	91 (*R*)[e]
3[f]	 **5**	**L2**	91	60 (*R*)
4	 **6**	**L2**	91	13 (*R*)

[a] Reaction conditions: aldehyde (0.1 mmol, 1.0 equiv.), R'Li (2.0 equiv.), (R_a,*S*)-**L2** (0.2 equiv.), TiCl(O*i*Pr)$_3$ (1.0 M in hexane, 2.8 equiv.) Et_2O, –20 °C, 10 min. [b] Isolated yield by flash chromatography. [c] Determined by chiral GC or HPLC. Configuration based on literature data (see Supporting Information for details). [d] Reaction conditions: aldehyde (0.1 mmol, 1.0 equiv.), TiCl(O*i*Pr)$_3$ (1 M in hexane, 3.2 equiv.), *n*BuLi (1.6 M in hexane, 2.5 equiv.), Et_2O, –20 °C. [e] Determined on the corresponding acetate derivative (see Supporting Information for details). [f] Reaction conditions: aldehyde (0.1 mmol, 1.0 equiv.), TiCl(O*i*Pr)$_3$ (1 M in hexane, 5.0 equiv.), *i*BuLi (1.7 M in heptane, 2.5 equiv.), Et_2O, –20 °C.

Conclusions

In conclusion, we have developed an efficient catalytic system for the enantioselective addition of alkyllithium reagents to aldehydes, in the presence of TiCl(O*i*Pr)$_3$ and employing Ar-BINMOL ligands as the chiral inductors. This novel methodology provides versatile carbinol units with a high level of enantiocontrol and in good yields under milder conditions than previously described methods. The chemoselectivity of the process is remarkable in that the addition of highly reactive organolithium reagents can be carried out in the presence of halogens and nitrile functionalities. Moreover, by employing lower titanium loadings, more practical reaction temperatures and shorter reaction times, we believe this methodology to be of potential use for a wide range of academic and industrial applications.

Experimental Section

To a stirred solution of **L1** or **L2** (0.20 equiv.) in Et_2O (0.06 M), $TiCl(O\textit{i}Pr)_3$ (2.8 equiv. 1M in hexane) was added at rt. The solution was stirred for 5 min and then cooled down to −20 ºC. Next, the organolithium reagent was added (2.0 equiv.) followed by immediate addition of the aldehyde (0.1 mmol). The reaction was stirred for 10 min and then quenched with water. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The reaction crude was purified by flash silica gel chromatography.

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Keywords: organolithium • titanium • Ar-BINMOL • aldehydes • enantioselective catalysis

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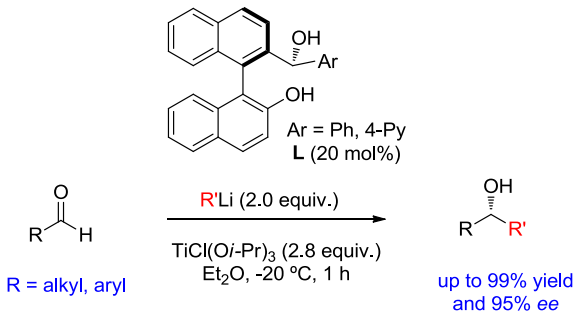
Entry for the Table of Contents

SHORT COMMUNICATION

Herein, we report an efficient catalytic system for the asymmetric alkylation of aldehydes with organolithium reagents in the presence of $TiCl(OiPr)_3$. A variety of alkyllithium reagents can be added to both aromatic and aliphatic aldehydes in good yields with high enantioselectivities in a simple one-pot procedure under mild conditions.



Asymmetric Synthesis

*M. Veguillas, R. Solà, L. Shaw and B. Maciá**

Page No. – Page No.

Catalytic Asymmetric Addition of Organolithium Reagents to Aldehydes

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