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SHORT COMMUNICATION

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Catalytic Asymmetric Addition of Alkyllithium Reagents to Aromatic Aldehydes

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Dedicated to the memory of Dr. Michael M. Pollard

Keywords: Asymmetric catalysis / Lithium / Aldehydes / Chirality / Titanium

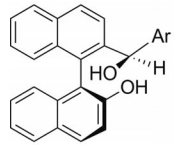
Herein, we report the first efficient catalytic system for the asymmetric alkylation of aldehydes with organolithium reagents in the presence of titanium(IV) isopropoxide. A variety of alkyllithium reagents can be added to aromatic aldehydes in good yields with high enantioselectivities in a simple one-pot procedure under mild conditions.

Introduction

Organolithium compounds are common bench reagents that can be found in any organic synthetic laboratory and are widely used in industry to produce numerous materials from pharmaceutical to polymers.[1] For catalytic applications, the low price and good availability of organolithium reagents make them desirable, but their high reactivity often precludes their use in more complex systems such as asymmetric C–C bond formation; (super) stoichiometric amounts of a chiral modifier and extremely low temperatures are usually required to obtain high enantioselectivity.[2] Only a few examples of asymmetric deprotonations,[3] addition to imines,[4] allylic alkylation reactions,[5] and addition of alkynes[6] have been described in the literature as catalytic processes for organolithium reagents.

The enantioselective addition of organometallic reagents to aldehydes is one of the most versatile methods for the synthesis of highly valuable chiral secondary alcohols.[7] Catalytic versions of this key transformation[8] have been studied extensively with organozinc reagents[9] and, only recently, with organomagnesium compounds.[10] However, for organolithium reagents, the progress is limited to their corresponding transmetalation into less reactive intermediates such as $RTi(iPrO)_3$[11] (alkyllithiums) and zinc[12] or magnesium derivatives[13] (aryllithiums), involving the problematic use of chelating additives and the tedious removal of the generated lithium salts. Only last year, a substoichiometric enantioselective addition of methyllithium to *o*-tolylbenzaldehyde was reported by Harrison-Marchand and Maddaluno.[14]

Recently, we described a highly enantioselective catalytic system, based on the readily available chiral ligand **L1** (Figure 1)[15] and an excess amount of titanium(IV) isopropoxide, for the addition of Grignard reagents to aldehydes.[10c] This result prompted us to examine this system in reactions with more challenging organolithium reagents. Herein, we report a simple one-pot methodology for the alkylation of aldehydes by using alkyllithium reagents and an excess amount of $Ti(iPrO)_4$ in the presence of catalytic amounts of ligand **L1** where no salt exclusion or additives are needed to achieve high enantioselectivities.



Ar = Ph,	(S_a,*R*)-**L1**
Ar = *o*-MeC_6H_4,	(S_a,*R*)-**L2**
Ar = *o*-$MeOC_6H_4$,	(S_a,*S*)-**L3**
Ar = *m*-$MeOC_6H_4$,	(S_a,*R*)-**L4**
Ar = *p*-$MeOC_6H_4$,	(S_a,*R*)-**L5**
Ar = *p*-FC_6H_4,	(S_a,*R*)-**L6**

Figure 1. Ar-BINMOLs ligands developed by Kiyooka, Lai, and Xu used in this study.

Results and Discussion

As a starting point, MeLi was chosen as a nucleophile based on the importance of methyl carbinol units in the synthesis of natural products and biologically active compounds.[16] Our first tests for the addition of MeLi to our model substrate benzaldehyde (**1a**) provided very promising results (Table 1). Desired alcohol **2a** was obtained with 90% enantioselectivity and 40% conversion when **1a** was added immediately after the addition of 1.5 equiv. of MeLi into a toluene solution containing 10 mol-% of **L1** and 4.5 equiv. of $Ti(iPrO)_4$ at –40 °C (Table 1, Entry 1). Both conversion

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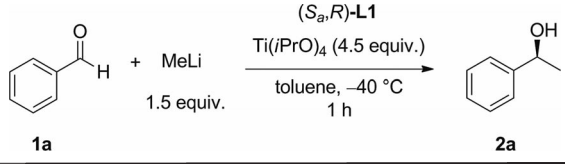
and enantioselectivity could be improved by increasing the catalyst loading up to 20 mol-% (63% conv., 93% *ee*; Table 1, Entry 2). However, changing the reaction temperature did not produce any better results; higher temperatures (–20 °C) led to lower *ee* values (Table 1, Entry 3), whilst lower temperatures (–60 °C) gave lower conversions (Table 1, Entry 4). It should be noted that the addition protocol had a significant influence on the outcome of the process. When MeLi was added last to the reaction mixture, the enantioselectivity dropped to 74% (Table 1, Entry 5). More interestingly, when substrate **1a** was added 15 min after the addition of MeLi to the reaction mixture containing the ligand and titanium tetraisopropoxide, the conversion drastically diminished to 19% (Table 1, Entry 6),[17] which indicates that the active species formed upon addition of MeLi to the **L1**-Ti(*i*PrO)$_4$ complex has a short life time at –40 °C.[18]

Table 1. Influence of catalyst loading, temperature, and addition protocol.[a]

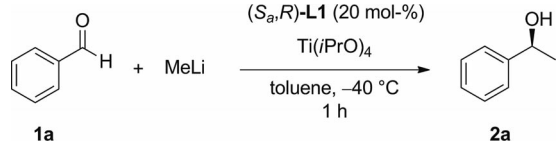


Entry	**L1** [mol-%]	*T* [°C]	Conv. [%][b]	*ee* [%][b]
1	10	–40	40	90
2	20	–40	63	93
3	20	–20	50	66
4	20	–60	20	84
5[c]	20	–40	63	74
6[d]	20	–40	19	86

[a] Conditions: **1a** (1 equiv., 0.07 M, added last), MeLi (1.6 M in Et_2O, 1.5 equiv.), (S_a,*R*)-**L1**, Ti(*i*PrO)$_4$ (4.5 equiv.), toluene, –40 °C, 1 h. [b] Determined by chiral GC (see the Supporting Information for details). [c] MeLi was added last. [d] Compound **1a** was added 15 min after the addition of MeLi.

In the second stage of the optimization process, we adjusted the amounts of MeLi and Ti(*i*PrO)$_4$. As shown in Table 2, lowering the ratio of Ti/Li to 2:1 had a beneficial effect on the enantioselectivity of the reaction, although the conversion obtained was slightly lower (Table 2, Entry 1 vs. 2). Equimolar Ti/Li amounts provided lower enantioselectivity and very poor conversion (Table 2, Entry 3). To improve the conversion, we decided to increase the equivalents of both MeLi and Ti(*i*PrO)$_4$, keeping the Ti/Li ratio close to the optimal 2:1. This strategy allowed the reaction to reach very good levels of conversion (85%) and enantioselectivity (94%; Table 2, Entry 4). Interestingly, when the reaction was performed in the absence or with catalytic amounts of Ti(*i*PrO)$_4$ (Table 2, Entry 5 and 6, respectively) full conversion but no enantioselectivity was observed. This seems to indicate that the active nucleophiles in the reaction are the organotitanium species generated in situ by transmetalation of the organolithium reagent with the excess amount of Ti(*i*PrO)$_4$.

Table 2. Li/Ti ratio optimization.[a]



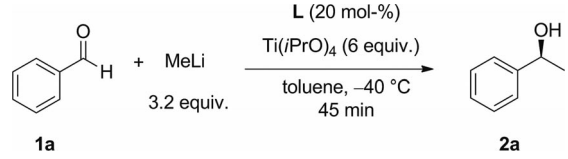
Entry	MeLi [equiv.]	Ti(*i*PrO)$_4$ [equiv.]	Ti/Li	Conv. [%][b]	*ee* [%][b]
1	1.5	4.5	3:1	63	93
2	1.5	3.0	2:1	59	96
3	1.5	1.5	1:1	23	89
4	3.2	6.0	1.9:1	85	94
5	1.5	–	–	>99	0
6	1.5	0.2	0.13:1	>99	0
7[c]	3.2	6.0	1.9:1	86	94

[a] Conditions: **1a** (0.1 mmol, 0.07 M), MeLi (1.6 M in Et_2O), (S_a,*R*)-**L1** (20 mol-%), Ti(*i*PrO)$_4$, toluene, –40 °C, 1 h. [b] Determined by chiral GC (see the Supporting Information for details). [c] Reaction was carried out in hexane.

Different solvents were also evaluated in the reaction (see the Supporting Information for further details), and although hexane proved to be equally effective as toluene (Table 2, Entry 7) its use was discarded to avoid possible solubility problems with other substrates.

Under these optimized conditions, we screened a small library of Ar-BINMOLs (Figure 1 and Table 3) as ligands for the addition of MeLi to benzaldehyde (**1a**). The results suggest that the stereochemical configuration of the ligand is of crucial importance (Table 3, Entry 1 vs. 2 and footnote c). Variation of the aromatic substituents (i.e., **L1**–**L6**) did not have a significant effect on either the conversion or the enantioselectivity (Table 3, Entry 1 vs. Entries 3–7), with the exception of *ortho*-methoxy-substituted (S_a,*S*)-**L3**, which provided lower conversion (Table 3, Entry 3).

Table 3. Ligand screening.[a]



Entry	Ar in **L**	**L**	Conv. [%][b]	*ee* [%][b]
1	Ph	(S_a,*R*)-**L1**	85	94
2	Ph	(S_a,*S*)-**L1**[c]	60	0
3	*o*-MeC$_6$H$_4$	(S_a,*R*)-**L2**	79	94
4	*o*-MeOC$_6$H$_4$	(S_a,*S*)-**L3**	15	93
5	*m*-MeOC$_6$H$_4$	(S_a,*R*)-**L4**	81	90
6	*p*-MeOC$_6$H$_4$	(S_a,*R*)-**L5**	84	86
7	*p*-FC$_6$H$_4$	(S_a,*R*)-**L6**	87	94

[a] Conditions: **1a** (0.1 mmol, 0.07 M), MeLi (1.6 M in Et_2O, 3.2 equiv.), **L** (20 mol-%), Ti(*i*PrO)$_4$ (6 equiv.), toluene, –40 °C, 45 min. [b] Determined by chiral GC (see the Supporting Information for details). [c] Same axial chirality as (S_a,*R*)-**L1** but opposite configuration at the sp^3 center.

The progress of the model reaction under optimal conditions was monitored by GC (Figure 2, profile a) and compared with the reaction progress in the absence of the ligand

(Figure 2, profile b) or in the presence of 20 mol-% of (*S*)-BINOL as ligand (Figure 2, profile c).[19] A pronounced acceleration of the reaction rate was observed when the Ti(*i*PrO)$_4$-**L1** complex was used and 92% of conversion was reached in only 45 min, in contrast with the 80% conversion that the blank reaction achieved in 90 min or the 79% conversion that the Ti(*i*PrO)$_4$-BINOL complex provided after 10 h of reaction.[20]

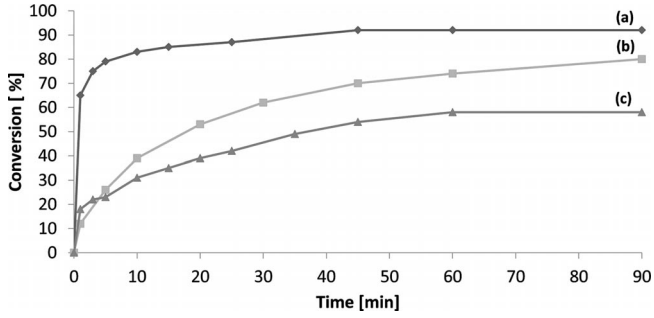


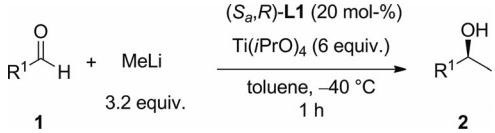
Figure 2. Progress of the model reaction in toluene at –40 °C: (a) **1a**, MeLi (3.2 equiv.), (S_a,*R*)-**L1** (20 mol-%), Ti(*i*PrO)$_4$ (6 equiv.); (b) **1a**, MeLi (3.2 equiv.), Ti(*i*PrO)$_4$ (6 equiv.); (c) **1a**, MeLi (3.2 equiv.), (*S*)-BINOL (20 mol-%), Ti(*i*PrO)$_4$ (6 equiv.). Conversion determined by GC.

The scope of the addition of MeLi was then examined with different aldehydes (Table 4). The new catalytic system described above proved to be remarkably efficient; a versatile range of methyl carbinol units was prepared in good yield (74 to 91%) and enantioselectivity (72 to 90%)[21] from a wide range of substrates bearing electron-poor or electron-rich substituents at the *meta* and *para* positions (Table 4, Entries 1, 3–8). The lower yield and selectivity of *o*-methylbenzaldehyde (Table 4, Entry 2) might be ascribed to higher steric hindrance around the reactive site.

The tolerance of this methodology towards functionalized substrates should be emphasized: chloro and cyano functionalities showed resistance to the very reactive lithium reagents when used under these reaction conditions (Table 4, Entries 7 and 8). The reactions with 2-naphthaldehyde and the heteroaromatic substrates 2-thiophenecarboxaldehyde and 2-furaldehyde gave 90, 88, and 72% *ee*, respectively, along with very good yields (Table 4, Entries 9–11), whereas cinnamic aldehyde provided a moderate enantioselectivity (Table 4, Entry 12). Remarkably, all reactions were finished in less than 1 h without any byproduct formation. Moreover, the unreacted starting material and ligand could be easily recovered, and the latter, could be recycled and reused without any loss of activity.[20] Regarding aliphatic substrates, phenylacetaldehyde (Table 4, Entry 13) gave low conversion and moderate enantioselectivity, whereas the addition of MeLi to pivaldehyde (Table 4, Entry 14) proceeded in less than 2% conversion.

Finally, we turned our attention to other alkyllithium reagents (Table 5). Gratifyingly, the addition of other linear reagents like EtLi and *n*BuLi proceeded in good yield (62 to 90%) and enantioselectivity (90 to 96%) for a wide range of aromatic aldehydes bearing electron-donating or -withdrawing groups (Table 5, Entries 1–8). It was also noted that (i) an increase in the size of the nucleophile meant an improvement in the enantioselectivity (Table 5, Entries 1–3 vs. 4–8); (ii) no evidence of common lithium–halogen exchange was found when halogenated aldehydes were used as substrates (Table 5, Entries 5 and 6); (iii) labile functionalities like carbonates were tolerated, as demonstrated by

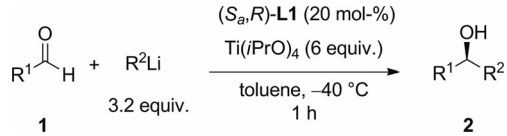
Table 4. Asymmetric addition of MeLi to aldehydes: scope of the reaction.[a]



Entry	R^1	Yield [%][b]	*ee* [%][c]
1	Ph	87	90 (*S*)
2	*o*-MeC$_6$H$_4$	78	62 (*S*)
3	*m*-MeC$_6$H$_4$	87	82 (*S*)
4	*p*-MeC$_6$H$_4$	81	88 (*S*)
5	*p*-MeOC$_6$H$_4$	91	89 (*S*)
6	*p*-CF$_3$C$_6$H$_4$	82	88 (*S*)
7	*p*-ClC$_6$H$_4$	74	84 (*S*)
8	*p*-CNC$_6$H$_4$	84	82 (*S*)
9	2-naphthyl	85	90 (*S*)
10	2-thienyl	57 (90)[d]	88 (*S*)
11	2-furyl	56 (86)[d]	72 (*S*)
12	PhCH=CH	84	68 (*S*)
13	PhCH$_2$	23	62 (*S*)
14	*t*Bu	<2	nd[e]

[a] Conditions: **1** (0.3 mmol, 1 equiv., 0.12 M), MeLi (1.6 M in Et$_2$O, 3.2 equiv.), (S_a,*R*)-**L1** (20 mol-%), Ti(*i*PrO)$_4$ (6 equiv.), toluene, –40 °C, 1 h. [b] Isolated yield after flash chromatography. [c] Determined by chiral GC or HPLC. Absolute configuration determined by correlation with known compounds (see the Supporting Information for details). [d] Volatile products, conversions based on GC data in brackets. [e] Not determined.

Table 5. Asymmetric addition of alkyllithium to aldehydes: scope of the reaction.[a]



Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	Ph	Et	78	92 (*S*)
2	*p*-MeC$_6$H$_4$	Et	66	90 (*S*)
3	*p*-ClC$_6$H$_4$	Et	62	92 (*S*)
4	Ph	*n*Bu	90	96 (*S*)
5	*p*-BrC$_6$H$_4$	*n*Bu	89	94 (*S*)
6	*p*-ClC$_6$H$_4$	*n*Bu	85	92 (*S*)
7	*p*-MeOC$_6$H$_4$	*n*Bu	89	94 (*S*)
8	*p*-MeOCO$_2$C$_6$H$_4$	*n*Bu	90	96 (*S*)
9	2-naphthyl	Ph	96	17 (*S*)
10	cyclohexyl	Ph	92	39 (*R*)

[a] Conditions: **1** (0.3 mmol, 1 equiv., 0.12 M), R^2Li (3.2 equiv.), (S_a,*R*)-**L1** (20 mol-%), Ti(*i*PrO)$_4$ (6 equiv.), toluene, –40 °C, 1 h. [b] Isolated yield after flash chromatography. [c] Determined by chiral GC or HPLC. Absolute configuration determined by correlation with known compounds (see the Supporting Information for details).

the reaction of 4-formylphenyl methyl carbonate (Table 5, Entry 8). Interestingly, the use of the sp^2-hybridized phenyllithium reagent (PhLi) provided very good yield but low and moderate enantioselectivities in the addition to 2-naphthaldehyde and cyclohexanecarbaldehyde, respectively (Table 5, Entries 9 and 10). A limitation of this methodology is highlighted by the reaction of bulky *i*BuLi with benzaldehyde (**1a**), which gave 40% conversion into the reduction product fenilmethanol, and corresponding alcohol **2** was formed in 8% yield with 62% *ee*.

Conclusions

In conclusion, we have developed the first efficient enantioselective catalytic system for the addition of alkyllithium reagents to aromatic aldehydes by using an excess amount of titanium tetraisopropoxide. This methodology allows the preparation of highly valuable optically active alcohols from economical and commercially available lithium reagents. Reactions are performed in a simple and fast one-pot procedure and no salt exclusion is needed. Moreover, the potential problems associated with the high reactivity of organolithium compounds are overcome under these reaction conditions, as this methodology proves to be compatible with functionalized substrates. 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)$_4$ (550 μL, 6 equiv., 1.8 mmol) was added to the solution at –40 °C. After 5 min, RLi (3.2 equiv., 0.96 mmol) was added followed by rapid addition of the aldehyde (0.3 mmol). The reaction mixture was stirred at –40 °C for 1 h and then quenched with H_2O (2 mL) and 2 M HCl (2 mL). The crude product was extracted with EtOAc (3 × 5 mL), and the combined organic layer was 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 alcohol **2**.

Supporting Information (see footnote on the first page of this article): General procedures, characterization data, ^{1}H NMR and ^{13}C NMR spectra, GC and HPLC chromatograms.

Acknowledgments

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[17] 81% of the starting material could be detected by CG.

[18] If **1a** is added to the reaction mixture 30 min after the addition of MeLi, the conversion is <5%.

[19] Compound **2a** was obtained with 7%*ee* when BINOL was used as the ligand.

[20] See the Supporting Information for details and extra data.

[21] Scaling up from 0.1 to 0.3 mmol of substrate did not have any significant effect on the outcome of the reaction. Only for the addition of MeLi to benzaldehyde did the conversion increase from 85 to 92% and the enantioselectivity diminish from 94 to 90% (Table 2, Entry 4 vs. Table 4, Entry 1).

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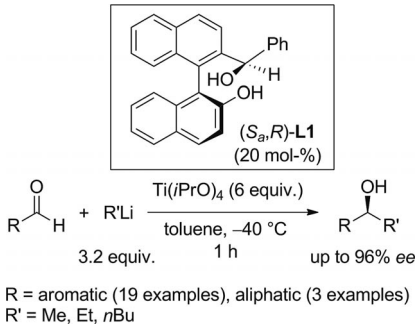
Asymmetric Catalysis

Herein, we report the first efficient catalytic system for the asymmetric alkylation of aldehydes with organolithium reagents in the presence of titanium(IV) isopropoxide. A variety of alkyllithium reagents can be added to aromatic aldehydes in good yields with high enantioselectivities in a simple one-pot procedure under mild conditions.



Keywords: Asymmetric catalysis / Lithium / Aldehydes / Chirality / Titanium

